Description

Inhibitors of Anthrax Lethal Factor

Field of the Invention

The present invention relates to the prophylaxis and treatment of anthrax infections and, more particularly, to compounds that act as specific inhibitors of Anthrax Lethal Factor (LF) activity, methods and means for making such inhibitors and their use as pharmaceuticals.

Background of the Invention

Anthrax is a zoonotic illness recognized since antiquity. In the 1870s, Robert Koch demonstrated for the first time the bacterial origin of a specific disease, with his studies on experimental anthrax, and also discovered the spore stage that allows persistence of the organism in the environment. Shortly afterward, *Bacillus anthracis* was recognized as the cause of woolsorter disease (inhalational anthrax). William Greenfield's successful immunization of livestock against anthrax soon followed in 1880, although Louis Pasteur's 1881 trial of a heat-cured anthrax vaccine in sheep is usually remembered as the initial use of a live vaccine.

Human cases of anthrax are invariably zoonotic in origin, with no convincing data to suggest that human-to-human transmission has ever taken place. Primary disease takes one of three forms: (1) Cutaneous, the most common, results from contact with an infected animal or animal products; (2) Inhalational is much less common and a result of spore deposition in the lungs, while (3) Gastrointestinal is due to ingestion of infected meat. Most literature cites cutaneous disease as constituting the large majority (up to 95%) of cases.

Bacillus anthracis is a large, gram-positive, sporulating rod, with square or concave ends. Growing readily on sheep blood agar, *B. anthracis* forms rough, gray-white colonies of four to five mm, with characteristic comma-shaped or "comet-tail" protrusions. Several tests are helpful in differentiating *B. anthracis* from other *Bacillus* species. *Bacillus anthracis is* characterized by an absence of the following: Hemolysis, motility, growth on phenylethyl alcohol blood agar, gelatin hydrolysis, and salicin fermentation. *Bacillus anthracis* may also be identified by the API-20E and API-50CHB systems used in conjunction with the previously mentioned biochemical tests. Definitive identification is based on immunological demonstration of the

production of protein toxin components and the poly-D-glutamic acid capsule, susceptibility to a specific bacteriophage, and virulence for mice and guinea pigs.

The virulence of *B anthracis* is dependent on two toxins, lethal toxin and edema toxin, as well as on the bacterial capsule. The importance of a toxin in pathogenesis was demonstrated in the early 1950s, when sterile plasma from anthrax-infected guinea pigs caused disease when injected into other animals (Smith, H. and J. Keppie, *Nature* **173**:869-870 (1954)). It has since been shown that the anthrax toxins are composed of three entities, which in concert lead to some of the clinical effects of anthrax (Stanley, J.L. and H. Smith, *J. Gen Microbiol* **26**:49-66 (1961); Beall, F.A. *et al.*, *J. Bacteriol* **83**:1274-1280 (1962)). The first of these, protective antigen, is an 83kd protein so named because it is the main protective constituent of anthrax vaccines. The protective antigen binds to target cell receptors and is then proteolytically cleaved of a 20kd fragment. A second binding domain is then exposed on the 63kd remnant, which combines with either edema factor, an 89kd protein, to form edema toxin, or lethal factor, a 90kd protein, to form lethal toxin (Leppla, S.H. *et al.*, *Salisbury Med Bull Suppl.*, **68**:41-43 (1990)). The respective toxins are then transported across the cell membrane, and the factors are released into the cytosol where they exert their effects. Edema factor, a calmodulin-dependent adenylate cyclase, acts by converting adenosine triphosphate to cyclic adenosine monophosphate. Intracellular cyclic adenosine monophosphate levels are thereby increased, leading to the edema characteristic of the disease (Leppla, S.H., *Proc Natl Acad Sci USA* **79**:3162-3166 (1982)). The action of lethal factor, believed to be a metalloprotease, is less well understood. Lethal toxin has been demonstrated to lyse macrophages at high concentration, while inducing the release of tumor necrosis factor and interleukin 1 at lower concentrations (Hanna, P.C. *et al.*, *Proc Natl Acad Sci USA* **90**:10198-10201 (1993); Freidlander, A.M., *J Biol Chem.* **261**:7123-7126 (1986)).

It has been shown that a combination of antibodies to interleukin 1 and tumor necrosis factor was protective against a lethal challenge of anthrax toxin in mice, as was the human interleukin 1 receptor antagonist (Hanna, P.C. *et al.*, *Proc Natl Acad Sci USA* **90**:10198-10201 (1993)). Macrophage-depleted mice were shown to resist lethal toxin challenge, but to succumb when macrophages were reconstituted. The genes for both the toxin and the capsule are carried by plasmids, designated pXO1 [33] and pX02, respectively (Green, B.D. *et al.*, *Bacillus anthracis Infect Immunol.* **49**:291-297 (1985); Uchida, I. *et al.*, *J Gen Microbiol.* **131**:363-367 (1985)).

Disease occurs when spores enter the body, germinate to the bacillary form, and multiply. In cutaneous disease, spores gain entry through cuts, abrasions, or in some cases through certain species of biting flies. Germination is thought to take place in macrophages, and toxin release results in edema and tissue necrosis but little or no purulence, probably because of inhibitory effects of the toxins on leukocytes. Generally, cutaneous disease remains localized, although if untreated it may become systemic in up to 20% of cases, with dissemination via the lymphatic system. In the gastrointestinal form, *B. anthracis is* ingested in spore-contaminated meat, and may invade anywhere in the gastrointestinal tract. Transport to mesenteric or other regional lymph nodes and replication occur, resulting in dissemination, bacteremia, and a high mortality rate. As in other forms of anthrax, involved nodes show an impressive degree of hemorrhage and necrosis.

The pathogenesis of inhalational anthrax is more fully studied and understood. Inhaled spores are ingested by pulmonary macrophages and carried to hilar and mediastinal lymph nodes, where they germinate and multiply, elaborating toxins and overwhelming the clearance ability of the regional nodes. Bacteremia occurs, and death soon follows.

Penicillin remains the drug of choice for treatment of susceptible strains of anthrax, with ciprofloxacin and doxycycline employed as suitable alternatives. Some data in experimental models of infection suggest that the addition of streptomycin to penicillin may also be helpful. Penicillin resistance remains extremely rare in naturally occurring strains; however, the possibility of resistance should be suspected in a biological warfare attack. Cutaneous anthrax may be treated orally, while gastrointestinal or inhalational disease ordinarily should receive high doses of intravenous antibiotics (penicillin G, 4 million units every 4 hours; ciprofloxacin, 400 mg every 12 hours; or doxycycline hyclate, 100 mg every 12 hours). The more severe forms require intensive supportive care and have a high mortality rate despite optimal therapy. The use of anti-anthrax serum, while no longer available for human use except in the former Soviet Union, was thought to be of some use in the pre-antibiotic era, although no controlled studies were performed.

Although anthrax vaccination dates to the early studies of Greenfield and Pasteur, the "modern" era of anthrax vaccine development began with a toxin-producing, unencapsulated (attenuated) strain in the 1930s. Administered to livestock as a single dose with a yearly booster, the vaccine was highly immunogenic and well tolerated in most species, although somewhat

virulent in goats and llamas. This preparation is essentially the same as that administered to livestock around the world today. The first human vaccine was developed in the 1940s from nonencapsulated strains. This live spore vaccine, similar to Sterne's product, is administered by scarification with a yearly booster. Studies show a reduced risk of 5-to-15-fold in occupationally exposed workers (Shlyakhov, E.N and E. Rubenstein, *Vaccine* **12**:727-730 (1994)).

British and U.S. vaccines were developed in the 1950s and early 1960s, with the U.S. product an aluminum hydroxide-adsorbed, cell-free culture filtrate of an unencapsulated strain (V770-NP1-R), and the British vaccine an alum-precipitated, cell-free filtrate of a Sterne strain culture. The U.S. vaccine has been shown to induce high levels of antibody only to protective antigen, while the British vaccine induces lower levels of antibody to protective antigen but measurable antibodies against lethal factor and edema factor (Turnbull, P.C.B. *et al.*, *Infect Immunol.* **52**:356-363 (1986); Turnbull, P.C.B. *et al.*, *Med Microbiol Immunol.* **177**:293-303 (1988)). Neither vaccine has been examined in a human clinical efficacy trial. A high number of the recipients of the vaccine have reported some type of reaction to vaccination. The preponderance of these events was minor. Manufacturer labeling for the current Michigan Department of Public Health anthrax vaccine adsorbed (AVA) product cites a 30% rate of mild local reactions and a 4% rate of moderate local reactions with a second dose. The current complex dosing schedule for the AVA vaccine consists of 0.5mL administered subcutaneously at 0, 2, and 4 weeks, and 6, 12, and 18 months, followed by yearly boosters.

Animal studies examining the efficacy of available anthrax vaccines against aerosolized exposure have been performed. While some guinea pig studies question vaccine efficacy, primate studies have support its role. In recent work, rhesus monkeys immunized with 2 doses of the AVA vaccine were challenged with lethal doses of aerosolized B *anthracis* spores. All monkeys in the control group died 3 to 5 days after exposure, while the vaccinated monkeys were protected up to 2 years after immunization (Ivins, B.E. *et al.*, *Salisbury Med Bull Suppl.* **87**:125-126 (1996)). Another trial used the AVA vaccine in a 2-dose series with a slightly different dosing interval, and again found it to be protective in all rhesus monkeys exposed to lethal aerosol challenge (Pitt, M.L.M. *et al.*, *Salisbury Med Bull Suppl.* **87**:130 (1996)). Thus, available evidence suggests that two doses of the current AVA vaccine should be efficacious against an aerosol exposure to anthrax spores. In addition, a highly purified, minimally reactogenic, recombinant protective antigen vaccine has been investigated, using aluminum as well as other

adjuvants. Other approaches include cloning the protective antigen gene into a variety of bacteria and viruses, and the development of mutant, avirulent strains of *B anthracis*. One significant limitation on the use of vaccines is that existing vaccines provide no protection against a number of strains of *B. anthracis*.

Recent incidents, such as the suspected use of biological and chemical weapons during the Persian Gulf War, underscore the threat of biological warfare either on the battlefield or by terrorists. Anthrax has been the focus of much attention as a potential biological warfare agent for at least six decades, and modeling studies have shown the potential for use in an offensive capacity. Dispersal experiments with the simulant *Bacillus globigii* in the New York subway system in the 1960s suggested that release of a similar amount of *B. anthracis* during rush hour would result in 10,000 deaths. On a larger scale, the World Health Organization estimated that 50kg of *B anthracis* released upwind of a population center of 500,000 would result in up to 95,000 fatalities, with an additional 125,000 persons incapacitated (Huxsoll, D.L. *et al.*, *JAMA* **262**:677-679 (1989)). Both on the battlefield and in a terrorist strike, *B. anthracis* has the attribute of being potentially undetectable until large numbers of seriously ill individuals present with characteristic signs and symptoms of inhalational anthrax.

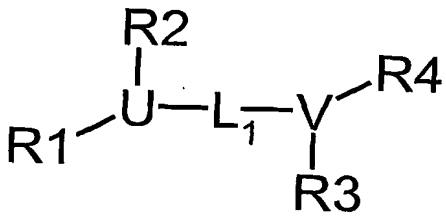
Given these findings, efforts to prevent the disease or to ameliorate or treat its effects are of obvious importance. The U.S. military's current M17 and M40 gas masks provide excellent protection against the 1 to 5μm particulates needed for a successful aerosol attack. Assuming a correct fit, these masks would be highly effective if in use at the time of exposure. Some protection might also be afforded by various forms of shelter. The pre-exposure use of the current AVA anthrax vaccine, which is approved by the U.S. Food and Drug Administration, appears to be an important adjunct. Results of primate studies also support the concept of post-exposure antibiotic prophylaxis. One study showed that 7 of 10 monkeys given penicillin, 8 of 9 given ciprofloxacin, 9 of 10 treated with doxycycline, and all 9 receiving doxycycline plus post-exposure vaccination survived a lethal aerosol challenge, with all animals receiving antibiotics for 30 days following exposure (Friedlander, A.M. *et al.*, *J Infect Dis.* **167**:1239-1242 (1993). Earlier research suggested that short courses of prophylactic antibiotics delayed but did not prevent clinical disease (Henderson, D.W. *et al.*, *J Hyg.* **54**:28-36 (1956). Accordingly, in the event of documented exposure, prolonged prophylactic antibiotic use, as well as vaccination, would be mandatory. In the biological warfare setting, the differential diagnosis of inhalational

anthrax would include plague and tularemia. Fluoroquinolones also have activity against these diseases, supporting the use of ciprofloxacin and perhaps other drugs of this class as either a pre-exposure or post-exposure measure.

It is therefore apparent that while certain prophylactic and treatment schemes may prove useful in preventing or ameliorating anthrax infections, there remains a compelling need to improve the arsenal of techniques and agents available for this purpose.

Disclosure of the Invention

The present invention provides methods, compounds and compositions for inhibiting Anthrax Lethal Factor activity, and for preventing and/or treating anthrax infections. In one aspect, the invention provides a compound in accordance with the formula:



Wherein **U** and **V** are, independently, C, N, or $C(CH_3)$, **L1** is a linker and **R1**, **R2**, **R3** and **R4** are each independently selected substituent groups as hereinafter more fully defined.

Other aspects of the present invention provide pharmaceutical compositions comprising such compounds, and methods of synthesizing and using such compounds and compositions in prophylactic and treatment schemes useful in preventing or ameliorating anthrax infections.

Brief Description of the Drawing

Figure 1 is a graphic depiction of selected compounds of the present invention, together with comparitive activities in inhibiting LF and MMP1.

Detailed Description of the Invention

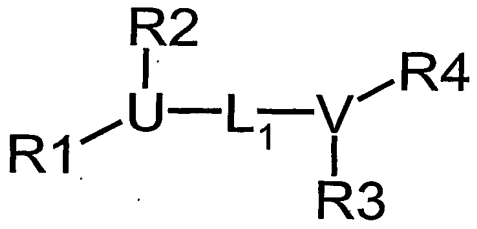
The present invention provides methods, compounds and compositions for treating anthrax infections by inhibiting Anthrax Lethal Factor (LF) activity. The novel compositions for use herein are LF inhibitors. These substances function by binding to the LF cleavage site, and preventing the LF from catalyzing its physiological substrate. LF inhibitors are useful, either alone or together with other therapeutic compositions, in the prevention and treatment of anthrax infections. Although the term "infection" is ordinarily used in its epidemiological sense, it will readily be recognized that "infections" by *Bacillus anthracis* spp., or invasions by LF, can occur naturally or be purposefully induced.

Anthrax toxin, produced by *Bacillus anthracis*, is composed of three proteins: Protective antigen (PA), edema factor (EF) and LF. Protective antigen is an 83kd protein that binds to specific cell surface receptors and is then proteolytically activated to a 63kd fragment (PA63), which forms a membrane channel that mediates entry of EF or LF into the cell. PA combines with either EF, an 89kd protein, to form edema toxin, or LF, a 90kd protein, to form lethal toxin (Leppla, S.H. *et al.*, *Salisbury Med Bull Suppl.*, **68**:41-43 (1990)). The respective toxins are then transported across the cell membrane, and the factors are released into the cytosol where they exert their effects. EF, a calmodulin-dependent adenylate cyclase, acts by converting adenosine triphosphate to cyclic adenosine monophosphate. Intracellular cyclic adenosine monophosphate levels are thereby increased, leading to the edema characteristic of the disease (Leppla, S.H., *Proc Natl Acad Sci USA* **79**:3162-3166 (1982)).

The action of LF, the dominant virulence factor produced by *Bacillus anthracis*, and believed to be a metalloprotease, is less well understood. Lethal toxin has been demonstrated at high concentration to lyse macrophages, while inducing the release of tumor necrosis factor and interleukin 1 at lower concentrations (Hanna, P.C. *et al.*, *Proc Natl Acad Sci USA* **90**:10198-10201 (1993); Freidlander, A.M., *J Biol Chem.* **261**:7123-7126 (1986)). LF is a 776 amino acid protein that contains a putative zinc-binding site (HEFGF) at residues 686-690, a characteristic of metalloproteases. Mutation of the H or E residues is reported to inactivate LF, and reduces its zinc-binding activity.

One useful approach to providing agents, which will serve as inhibitors of LF activity, is to model the protein surface structure of MAP kinase kinase 1 (MAPKK1), a physiological substrate cleaved by LF. In conjunction, the consensus structural features of MAPKK1 and MAPKK2 that contain the LF cleavage site will provide a basis for designing non-peptide inhibitors of LF activity.

Thus, in one aspect, the invention provides a compound in accordance with the formula:



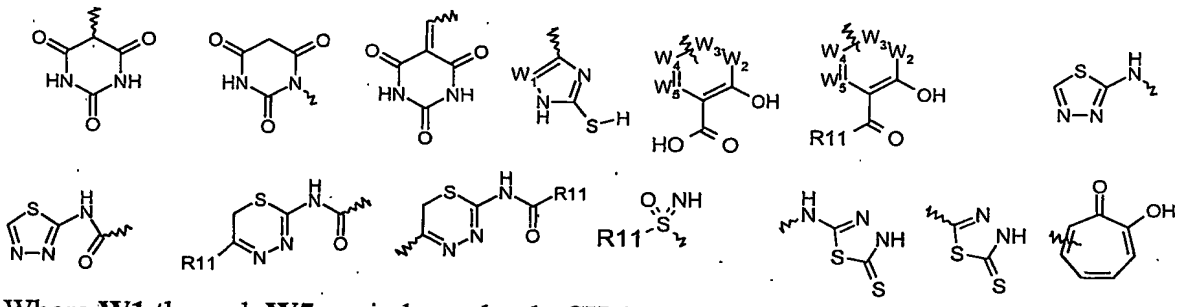
Wherein **U** and **V** are, independently, C, N, or $C(CH_3)$, **L1** is a linker and **R1**, **R2**, **R3** and **R4** are each independently selected substituent groups as hereinafter more fully defined:

R1 is $\mathbf{Z}(CH\mathbf{R5})_n\mathbf{Y}$ where n = 0 to 4, **Z** is a bond, S, CO, O, SO, SO_2, NH, N**R11**, SO_2N**R11**, N**R11**SO_2, 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-cyclohexylidene; **Y** is a group known to bind to zinc, including CON**R11**OH, COOH, SH, ArSH, $NHCOCH_2SH$, 2-hydroxybenzoate (linked at the 3,4,5, or 6-position), 2-hydroxypyridinecarboxylate (linked at the 3,4,5, or 6-position, with the ring nitrogen at any unsubstituted position), $CF_2P{=}O(OH)_2$, $C(CH_3){=}NOCH_2COOH$, $C(CH_2OH){=}NOCH_2COOH$, $NHCO(CH\mathbf{R11})_mSH$ (where m = 1 to 4), $PO(OH)_2$, PO(**R11**)OH, SO_2N**R11**OH, or NH(OH)CO**R11**.

Additional structures for **Y** are shown in Figure A. **Y** can optionally be derivatized to form a prodrug that is capable of undergoing conversion to a zinc-binding moiety after administration of the agent to a mammal. For example, SCO**R11** (as a prodrug for SH), COO**R11** (as a prodrug for COOH), $C{=}OOCH_2OC{=}O\mathbf{R11}$ (as a prodrug for COOH), C=ON**R11**OC=O**R11** (as a prodrug for C=ON**R11**OH).

R5 and **R11** are, independently, H, CH_3, amino, hydroxy, alkoxy, alkylthio, alkyl (C2-C10), branched alkyl (C3-C10), alkylthio (C1-C7), alkylthioalkyl (C2-C8), arylthio, alkylamino(C1-C7), amino, arylamino, aryl, heteroaryl, arylalkyl, heterarylalkyl, arylalkenyl, heterarylalkenyl, arylalkynyl, or heterarylalkynyl.

R1 is optionally further substituted with one or more of the following: NH_2, OH, halogen, alkyl, $CONH_2$, CONHOH, $C(NH)NH_2$, C(NH)NHOH, $NHC(NH)NH_2$, CN, NO_2, N**R6R7** where **R6** and **R7** are H or alkyl and optionally form a ring. **R5** can optionally form a ring with **R2** or with **R11**.



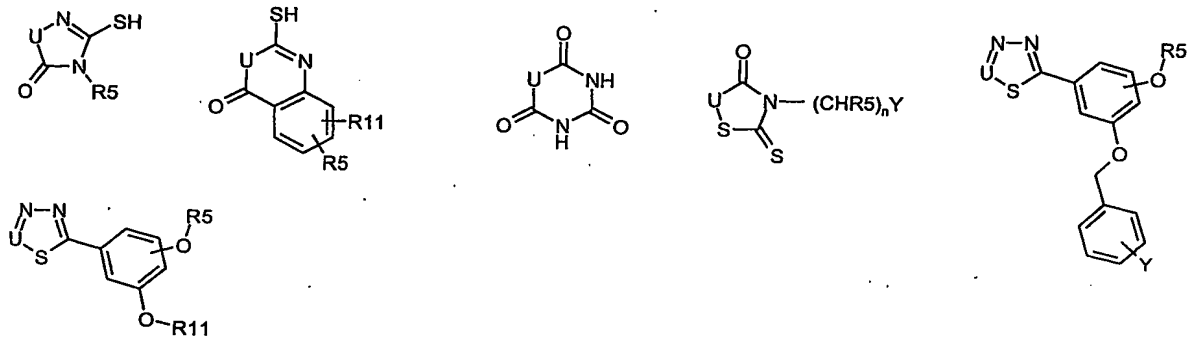
Where **W1** through **W5** are independently CH, N, C-alkyl, C-OH, CF, CCl, CCF_3, $COCF_3$, $COCH_3$, or CBr.

Figure A

R2 is H, isobutyl, n-butyl, pentyl, methyl, alkyl (C1-C10), branched alkyl (C3-C10), cycloalkyl, cycloalkylmethyl (C3-C9 cycle), $Ar(CH_2)n$ (where n = 0 to 4, Ar is phenyl, aryl, heteroaryl), phenethyl, arylalkenyl, heterarylalkenyl, arylalkynyl, heterarylalkynyl, alkenyl (C2-C8), alkynyl (C2-C8), pentafluorophenoxyethyl, pentafluorophenylmethyl, cycloalkenyl (C4-C10), alkylthio, arylthio, alkylamino, arylamino, aryl, dichlorophenyl. **R2** can optionally form a ring with **R5**, **R11**, **L1**, or **R3**. **R2**, **R5** and **R11** are optionally substituted with one or more of the following: NH_2, OH, halogen, alkyl, CF_3, CF_3O, CF_3S, alkoxy, alkylthio, SO_2alkyl (C1-C4), $CONH_2$, CONHOH, $C(NH)NH_2$, CN, NO_2, C(NH)NHOH, $NHC(NH)NH_2$, or N**R6R7** where **R6** and **R7** are H or alkyl and optionally form a ring.

R1, **R2** and **U** can optionally form a ring, including but not limited to the structures depicted in Figure B.

R11 in Figures B, C and D can be H, ethyl, methyl, isobutyl, sec-butyl, phenyl, phenethyl, benzyl, phenethyl, indolylmethyl, benzoethiophenylmethyl, hydroxyalkyl, alkyl (C1-C10), branched alkyl (C3-C10), cycloalkyl (C3-C10), aryl, 1-arylethenyl, 2-arylethenyl, heteroaryl, arylalkyl, heteroarylalkyl.



U, R5, Y, and R11 are as defined in the text.

Figure B

R3 is H, phenethyl, alkyl (C1-C10), branched alkyl (C1-C10), aryl, phenyl substituted with aryl or heteroaryl at the 2-, 3-, or 4-positions, benzyloxy, pyrrolyl substituted with 1-2 aryl groups, 2-aryl-1,3,4 thiadiazolyl, heteroaryl (including thiophenyl), -**L2**Ar where Ar includes 1-naphthyl, 2-naphthyl, 4-phenylphenyl, 5-(2-thienyl)-2-thienyl, 4-(3'-methoxyphenyl)phenyl, 4-(4'-methoxyphenyl)phenyl, 3-indolyl, phenyl, t-butyl, indolyl 3-phenylphenyl, indolyl, 2,3-dimethyl-5-indolyl, benzothiophenyl, 4-(1,2,3-thiadiazol-4-yl)phenyl, 4-(2-thienyl)phenyl, 5-(2-pyridyl)-2-thienyl, 1-(2-napthyl)vinylaminoalkyl, N-hydroxybenzamidin-4-yl, 2-methylcarbazol-3-yl, 2-ethylcarbazol-3-yl, aryl or heteroaryl and **L2** is a linker chosen from the following, in both orientations: bond, CH_2, $(CH_2)_2$, CH_2NHCH_2, $CH_2CH_2CONHCH_2$, $CH_2CH_2CONHCH_2CH_2$, 1,1 vinylidene, 1,2-vinylidene, CO, $CH_2CH_2NHCH_2$, $CH_2CH_2CH_2NHCH_2$, $CH_2NHCH_2CH_2$, $(CH_2)q$ where q = 3 to 7, (CH**R9**)r where r = 1 to 7 and **R9** is independently H, alkyl (C1-C10), branched alkyl (C3-C10), cycloalkyl (C3-C10), cycloalkylalkyl (C4-C14), alkyl thio, amino, alkyl amino, dialkylamino, (CH**R9**)s**X**(CH**R9**)t where s + t = 0 to 8, **X** is O, S, CO, SO, SO_2,

NH, CONH, NHCO, SO_2NH, $NHSO_2$ or N**R9** and **R9** is independently H, alkyl (C1-C10), branched alkyl (C3-C10), cycloalkyl (C3-C10), cycloalkylalkyl (C4-C14), acyl, alkyl thio, amino, alkyl amino, or dialkylamino. **R9** also includes N-linked heterocycles such as piperidine, pyrroline, (1,2,3,4-)tetahydrobetacarbolin-2yl, **R15** is H, alkyl (C1-C4), branched alkyl (C3-C5), or cycloalkyl(C3-C5). Carbon-carbon single bonds in **R8** can optionally be substituted with double or triple bonds. **R3** can optionally form a ring with **R2**, **L1**, or **R4**. Such rings include, without limitation, those depicted in Figure C. **R3**, **R9** and **R15** are optionally further substituted with one or more of the following NH_2, OH, halogen, $N(CH_3)_2$, alkyl, CF_3, CF_3O, CF_3S, alkoxy, alkylthio, $CONH_2$, CONHOH, $C(NH)NH_2$, CN, NO_2, C(NH)NHOH, $NHC(NH)NH_2$, aryloxy, trifluoromethylphenyloxy, carboxyalkyl (C2-C8), (Carboxyphenyl)methylthio, carboxyalkylthio (C2-C8), carboxyphenyl, N**R6R7** where **R6** and **R7** are H or alkyl and optionally form a ring.

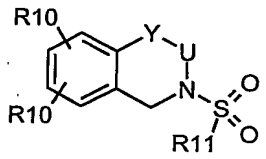


Figure C

R4 is H, alkyl (C1-C10), branched alkyl (C1-C10), arylalkyl, heteroarylalkyl, CON**R10R16** where **R10** is H, methyl, alkyl (C2-C10), branched alkyl (C3-C10), benzyl, phenethyl, arylalkyl, heteroarylalkyl, alkanoyl (C2-C8), branched alkanoyl, aroyl (C6-C12), heteroaroyl (C2-C10), isopropyl,CON**R16R12**; and where **R12** and **R16** are, independently, H, methyl, alkyl, benzyl, 2-phenylethyl, 2-indanyl, 2-morpholinylethyl, (2,6)-dimethoxylbenzyl, dimethylaminoethyl, (2-pyridyl)methyl, 2-(2-pyridyl)ethyl, 4-carboxybenzyl, 1-phenylethyl, $CH(CONH_2)CH_2C_6H_5$, $CH(CONH_2)CH_2CH(CH_3)_2$, $CH(CONH_2)CH(CH_3)CH_2CH_3$, $CH(CONH_2)CHCH_3$ $CH(CH_2OCH_3)CH_2C_6H_5$, $CH(CONHCH_2CH_2OCH_3)CH_2$cyclohexyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aminoalkyl, hydroxyalkyl, (trifluoromethylphenoxy)phenyl. N**R16R12** can optionally form an N-linked monocyclic or bicyclic heterocyclic ring, including but not limited to 1,2-dihydroisoindole, octahydroisoindole, morpholine, piperidine, piperazine, N-alkyl

piperazine (C1-C4), homopiperazine, 3-pyrroline, pyrrolidine, tetrahydroisoquinoline, octahydropyrrolo[3,4-C]pyrrole, L-proline, L-proline dimethylamide, D-proline, D-proline dimethylamide, and thiazolidine.

R4 can optionally form a ring with **L1** or **R3**. **R4**, **R6**, **R7**, **R10**, **R11**, **R12** and **R16** are optionally further substituted, independently, with 1 to 3 of the following substitutents: NH_2, OH, F, Cl, Br, methyl, alkyl, aryl, cycloalkyl (C3-C6), heterocycloalkyl, heteroaryl, CF_3, CF_3O, CF_3S, CF3, aryloxy, trifluoromethylphenoxy, alkoxy, alkylthio, $CONH_2$, CN, NO_2, CONHOH, $C(NH)NH_2$, C(NH)NHOH, $NHC(NH)NH_2$, N**R6R7** where **R6** and **R7** are H or alkyl and optionally form a ring.

R3 and **R4** can optionally form a ring, including but not limited to those depicted in Figure D.

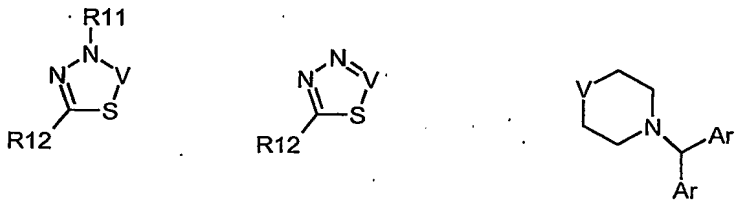


Figure D

L1 is a linker including the following, in either orientation: single bond, double bond, CONH, NHCO, $N(CH_3)CO$, $CON(CH_3)$, CH_2NH, $NHCH_2$, CH=CH,$C(NH_2)$=N, N=$C(NH_2)$, arylene (linked 1,2-; 1,3-; or 1,4), heteroarylene (linked 1,2-; 1,3-; or 1,4), ethynyl, CH=CF, CF=CH, CF=CF, CH_2CH_2, $C(CH_3)$=CH, CH=$C(CH_3)$, SO_2NH, SO_2, $COCH_2$, CH_2CO, $CNOHCH_2$, CH_2CNOH, $C(CF_3)$=CH, CH=$C(CF_3)$, SO_2CH_2, CH_2SO_2, $SOCH_2$, CH_2SO, CH_2CHOH, $CHOHCH_2$, lower cycloalkyl (C3-C6), or CHOHCHOH. **L1** is optionally substituted with one or more of the following: NH_2, OH, halogen, alkyl, CF_3, CF_3O, CF_3S, alkoxy, alkylthio, $CONH_2$, CONHOH, $C(NH)NH_2$, C(NH)NHOH, $NHC(NH)NH_2$, N**R6R7** where **R6** and **R7** are H or alkyl and optionally form a ring.

L1, **U** and **V** can optionally form a cycloaliphatic (C3-C6) or heterocyclic (4 to 6 atom) ring, optionally substituted with F, OCH_3, OH, or NH_2.

For all chiral centers on the scaffold, in the linker **L1**, and in substituents **R1** through **R4**, both R and S stereochemistry are contemplated. For all double bonds in the linker **L1**, and in substituents **R1** through **R4**, both E and Z stereochemistry are contemplated.

The symbol "Ar" represents any aryl group. "Aryl" includes phenyl, naphthyl, phenanthrenyl, anthracenyl, biphenyl, terphenyl, phenylnaphthyl and azulenyl linked from any position. "Heteroaryl" is any monocyclic, fused bicyclic or fused tricyclic aromatic system for which at least one ring atom is O, N, or S, including thiophene, pyrrole, noxazole, furan, thiazole, imidazole, pyrazole, isoxazole, isothiazole, oxadiazole, triazole, tetrazole, thidiazole, pyridazine, pyrimidine, pyrazine, thiadiazole, triazine, indolizine, indole, benzofuran, benzothiophene, benzimidazole, benzthiazole, purine, quinoline, isoquinoline, cinnoline, phtalazine, quinazoline, naphthyridine, pteridine, carbazole, acridine, phenazine, dibenzofuran, dibenzothiophene, isomers of these, and fused aromatic ring systems (up to 3 rings) containing these, heteroaryl-aryls (up to 4 rings), aryl-heteroaryls (up to 4 rings) and heteroaryl-heteroaryls (up to 4 rings) attached from any position. Examples of heteroaryl-aryls: thienylphenyl, pyridylnaphthyl. Examples of aryl heteroaryls: biphenylthiazolyl, napthyl pyrmidinyl.

All aromatic and heteroaromatic rings can be optionally and independently further substitutedwith one to four of the following groups: **R13**, **R13**O, **R13**S, **R13**CO, **R13**O-CO, **R13**SO, **R13**SO_2, **R13**SO_2NH, **R13**$NHSO_2$ in which **R13** is H, aryl, heteroaryl, NH_2, OH, halogen, alkyl (C1-C10), methyl, fluoro, chloro, bromo, iodo, heterocycloalkyl, heterocycloalkenyl, branched alkyl (C3-C8), cycloalkyl (C3-C8), bicycloalkyl (C4-C12), cycloalkenyl (C4-C9), bicycloalkenyl (C6-C12), arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, alkenyl, alkynyl, $CONH_2$, CONHOH, $C(NH)NH_2$, C(NH)NHOH, $NHC(NH)NH_2$, CN, NO_2, CF_3, OCF_3, SCF_3, CH_2CF_3, CH_3, perfluorinated alkyl (C1-C5), perfluorinated branched alkyl (C3-C5),

perfluorinated cyclic alkyl (C3-C5), alkyl (C1-C10), alkoxy (C1-C10), alkylthio (C1-C9), arylthio, heteroarylthio, arylalkylthio, 2'-hydroxyethoxy, alkoxycarbonylmethoxy (C1-C4), dialkylamino (C1-C4 where the 2 alkyls optionally form a heteroalicyclic ring), difluoromethoxy, guanidine, guanidinoalkyl (C1-C5), $H_2N(NH)C(CH_2)_h$ where h = 0 to 6, $H_2N(NH)CNHO(CH_2)_j$ where j = 0 to 6, (2-pyridyl)amino, (2-pyridyl)aminoalkyl (C1-C6), perfluoroalkyl (C1-C4), perfluoroalkylthio (C1-C4), perfluoroalkoxy (C1-C4), 2-carboxyvinyl, alkanoyl (C1-C5), alkoxycarbonyl (C1-C4), or alkanoylamino (C1-C8). **R13** may also be CON**R7R7** or N**R6R7** or SO_2N**R6R7** or N**R6**CO**R7** or N**R6**SO_2**R7** where **R6** and **R7** are, independently, H, alkyl (C1-C10), branched alkyl (C3-C8), cycloalkyl (C3-C8), aryl, arylalkyl, arylalkenyl, arylalkynyl, alkenyl, alkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, and where **R6** and **R7** optionally form a ring.

In the present disclosure, whenever a structure or substructure is depicted with 2two or more nominally identical groups Rn or Ar {e.g. **R5** in the substructure $Z(CHR5)_nY$ where n > 1}, each Rn or Ar represents, independently, the entire range of substitutents provided for Rn or Ar unless otherwise indicated.

Certain Preferred Embodiments

Among the numerous compounds described above as useful for inhibitiing LF activity, certain compounds are considered to be preferred due to one of more beneficial properties such as increased inhibitory activity, increases soulbility or bioavailability, persistance in vivo, ease of synthesis, and the like. Certain of such preferred compounds, and the compositions containing such compounds, include the following:

Compounds in the presently preferred embodiments will contain at least two ring moieties, either aromatic rings, heteroaromatic rings, or both aromatic and heteroaromatic rings. In the present embodiments **U** and **V** are, independently, C, N, or $C(CH_3)$.

R1 is $Z(CHR5)_nY$ where n is 0 to 4, **Z**= is a bond, S, CO, O, 1,2-phenylene, 1,3-phenylene, 1,4-phenylene; **Y** is a group known to bind to zinc, including CONR11OH,

COOH, 2-hydroxybenzoate (linked at the 3,4,5, or 6-position), 2-hydroxypyridinecarboxylate (linked at the 3,4,5, or 6-position, with the ring nitrogen at any unsubstituted position), $C(CH_3)=NOCH_2COOH$, or $C(CH_2OH)=NOCH_2COOH$. **Y** can optionally be derivatized to form a prodrug which is capable of undergoing conversion to a zinc-binding moiety after administration of the agent to a mammal. For example, **COOR11** (as a prodrug for COOH), $C=OOCH_2OC=OR11$ (as a prodrug for COOH), $C=ONR11OC=OR11$ (as a prodrug for C=ONR11OH). **R5** and **R11** are, independently, H, CH_3, amino, hydroxy, alkoxy, alkylthio, alkyl (C2-C10), butyl, isobutyl, methyl, branched alkyl (C3-C10), alkylthio (C1-C7), alkylthioalkyl (C2-C8), alkylamino(C1-C7), amino.

R1 is optionally further substituted with one or more of the following: NH_2, OH, halogen, alkyl, $CONH_2$, CONHOH, $C(NH)NH_2$, **NR6R7** where **R6** and **R7** are H or alkyl and optionally form a ring. **R5** can optionally form a ring with **R2** or with **R11**.

R2 is H, isobutyl, n-butyl, pentyl, methyl, alkyl (C1-C10), branched alkyl (C3-C10), cycloalkyl, cycloalkylmethyl (C3-C9 cycle), $Ar(CH_2)n$ (where n is 0 to 4, Ar=phenyl, aryl, heteroaryl), phenethyl, arylalkenyl, heterarylalkenyl, arylalkynyl, heterarylalkynyl, alkenyl (C2-C8), alkynyl (C2-C8), pentafluorophenoxyethyl, pentafluorophenylmethyl, cycloalkenyl (C4-C10), alkylthio, arylthio, alkylamino, arylamino, aryl, dichlorophenyl. **R2** can optionally form a ring with **R5**, **R11**, **L1**, or **R3**. **R2**, **R5** and **R11** are optionally substituted with one or more of the following: NH_2, OH, halogen, alkyl, CF_3, CF_3O, CF_3S, alkoxy, alkylthio, SO_2alkyl (C1-C4), $CONH_2$, CONHOH, $C(NH)NH_2$, CN, NO_2, C(NH)NHOH, $NHC(NH)NH_2$, or **NR6R7** where **R6** and **R7** are H or alkyl and optionally form a ring.

R1, **R2** and **U** can optionally form a ring, including the thiadiazole-containing structures in Figure B or a cycloaliphatic or heterocycloaliphatic ring. **R11** in Figure B is H, ethyl, methyl, isobutyl, phenethyl, benzyl, phenethyl, hydroxyalkyl, alkyl (C1-C10), branched alkyl (C3-C10), cycloalkyl (C3-C10), aryl, 1-arylethenyl, 2-arylethenyl, heteroaryl, arylalkyl, heteroarylalkyl.

R3 is H, phenethyl, alkyl (C1-C10), branched alkyl (C1-C10), aryl, phenyl substituted with aryl or heteroaryl at the 2-, 3-, or 4-positions, benzyloxy, pyrrolyl substituted with 1-2 aryl groups, 2-aryl-1,3,4 thiadiazolyl, heteroaryl (including thiophenyl), -**L2**Ar where Ar includes 1-naphthyl, 2-naphthyl, 4-phenylphenyl, 5-(2-thienyl)-2-thienyl, 4-(3'-methoxyphenyl)phenyl, 4-(4'-methoxyphenyl)phenyl, 3-indolyl, phenyl, t-butyl, indolyl 3-phenylphenyl, indolyl, 2,3-dimethyl-5-indolyl, benzothiophenyl, 4-(1,2,3-thiadiazol-4-yl)phenyl, 4-(2-thienyl)phenyl, 5-(2-pyridyl)-2-thienyl, 1-(2-napthyl)vinylaminoalkyl, N-hydroxybenzamidin-4-yl, 2-methylcarbazol-3-yl, 2-ethylcarbazol-3-yl, aryl or heteroaryl and **L2** is a linker chosen from the following, in both orientations: bond, CH_2, $(CH_2)_2$, CH_2NHCH_2, $CH_2CH_2CONHCH_2$, $CH_2CH_2CONHCH_2CH_2$, 1,1 vinylidene, 1,2-vinylidene, CO, (CH**R9**)r where r is 1 to 3 and **R9** is independently H, alkyl (C1-C10), branched alkyl (C3-C10), cycloalkyl (C3-C10), cycloalkylalkyl (C4-C14), alkyl thio, amino, alkyl amino, dialkylamino, (CH**R9**)s**X**(CH**R9**)t where s + t is 0 to 8, **X** is O, S, CO, NH, CONH, NHCO, SO_2NH, $NHSO_2$ or N**R9** and **R9** is independently H, alkyl (C1-C10), branched alkyl (C3-C10), cycloalkyl (C3-C10), cycloalkylalkyl (C4-C14), acyl, alkyl thio, amino, alkyl amino, or dialkylamino. **R9** also includes N-linked heterocycles such as piperidine, pyrroline, (1,2,3,4-)tetahydrobetacarbolin-2yl, **R15** is H, alkyl (C1-C4), branched alkyl (C3-C5), or cycloalkyl(C3-C5). Carbon-carbon single bonds in R8 can optionally be substituted with double or triple bonds. **R3** can optionally form a ring with **R2**, **L1**, or **R4**. Such rings include, but are not limited to, those depcted in Figure C. **R3**, **R9** and **R15** are optionally further substituted with one or more of the following NH_2, OH, halogen, $N(CH_3)_2$, alkyl, CF_3, CF_3O, CF_3S, alkoxy, alkylthio, $CONH_2$, CONHOH, $C(NH)NH_2$, CN, NO_2, C(NH)NHOH, $NHC(NH)NH_2$, aryloxy, trifluoromethylphenyloxy, carboxyalkyl (C2-C8), (Carboxyphenyl)methylthio, carboxyalkylthio (C2-C8), carboxyphenyl, N**R6R7** where **R6** and **R7** are H or alkyl and optionally form a ring.

R4 is H, alkyl (C1-C10), branched alkyl (C1-C10), arylalkyl, heteroarylalkyl, CON**R10R16** where **R10** is H, methyl, alkyl (C2-C10), branched alkyl (C3-C10), benzyl, phenethyl, arylalkyl, heteroarylalkyl, alkanoyl (C2-C8), branched alkanoyl, aroyl (C6-

C12), heteroaroyl (C2-C10), isopropyl, CONR16R12; and where R12 and R16 are, independently, H, methyl, alkyl, benzyl, 2-phenylethyl, 2-indanyl, 2-morpholinylethyl, (2,6)-dimethoxylbenzyl, dimethylaminoethyl, (2-pyridyl)methyl, 2-(2-pyridyl)ethyl, 4-carboxybenzyl, 1-phenylethyl, $CH(CONH_2)CH_2C_6H_5$, $CH(CONH_2)CH_2CH(CH_3)_2$, $CH(CONH_2)CH(CH_3)CH_2CH_3$, $CH(CONH_2)CHCH_3$ $CH(CH_2OCH_3)CH_2C_6H_5$, $CH(CONHCH_2CH_2OCH_3)CH_2$cyclohexyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aminoalkyl, hydroxyalkyl, (trifluoromethylphenoxy)phenyl. NR16R12 can optionally form an N-linked monocyclic or bicyclic heterocyclic ring, including but not limited to 1,2-dihydroisoindole, morpholine, piperidine, piperazine, N-alkyl piperazine (C1-C4), homopiperazine, 3-pyrroline, pyrrolidine, tetrahydroisoquinoline, L-proline dimethylamide, and D-proline dimethylamide. **R4** can optionally form a ring with **L1** or **R3**. **R4**, **R6**, **R7**, **R10**, **R11**, **R12** and **R16** are optionally further substituted, independently, with 1 to 3 of the following substitutents: NH_2, OH, F, Cl, Br, methyl, alkyl, aryl, cycloalkyl (C3-C6), heterocycloalkyl, CF_3, CF_3O, CF_3S, CF3, aryloxy, trifluoromethylphenoxy, alkoxy, alkylthio, $CONH_2$, CN, NO_2, CONHOH, $C(NH)NH_2$, C(NH)NHOH, $NHC(NH)NH_2$, NR6R7 where **R6** and **R7** are H or alkyl and optionally form a ring.

R3 and **R4** can optionally form a ring, including but not limited to those depicted in Figure D.

L1 is a linker including the following, in either orientation: single bond, double bond, CONH, NHCO, $N(CH_3)CO$, $CON(CH_3)$, CH_2NH, $NHCH_2$, CH=CH, arylene (linked 1,2-; 1,3-; or 1,4), heteroarylene (linked 1,2-; 1,3-; or 1,4), SO_2NH, SO_2, $COCH_2$, CH_2CO, $CNOHCH_2$, CH_2CNOH, SO_2CH_2, CHOHCHOH. **L1**, **U** and **V** can optionally form a cycloaliphatic (C3-C6) or heterocyclic (4 to 6 atom) ring, optionally substituted with F, OCH_3, OH, or NH_2.

For compounds in the most preferred embodiments, **U** and **V** are independently CH or CCH_3, **L1** is CONH or $CONCH_3$ in either orientation, **R1** is $CH_2CONHOH$,

$CH(CH_3)CONHOH$, $CH_2N(CHO)OH$, $CH(CH_3)N(CHO)OH$. **R2** is methyl, isobutyl, ethyl, n-propyl, n-butyl, cyclobutylmethyl, cyclopropylmethyl, 3-propenyl, 2-methyl-3-propenyl, 2-buten-1-yl, 2-butyn-1-yl, 3-propynyl, or cyclobutylmethyl substituted on the 3-position with methyl, ethyl, n-propyl, methoxy, hydroxymethyl, or aminomethyl. **R3** is **L2**Ar where **L2** is bond, or CH_2, $(CH_2)_2$, CO, or 1,1-vinylidene, and Ar is a group containing 2-3 aromatic/heteroaromatic rings (fused or directly linked). Ar can be naphthyl, benzothiophenyl, indolyl, quinolinyl, isoquinolinyl or carbazolyl linked from any free position, or a biaryl consisting of phenyl, thienyl, or pyridyl linked from any position and substituted on the 3 or 4 position with phenyl, pyridyl, thienyl, 3-substituted phenyl. The aromatic rings can be optionally further substituted with methoxy, methyl, fluoro, ethyl, hydroxyl, hydroxymethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, 2-dimethylaminoethyl, or 3-dimethylaminopropyl. **R4** is CON**R16R12** or CH_2CON**R16R12**, with **R12** is independently, H, benzyl, 2-phenylethyl, 2-indanyl, 2-morpholinylethyl, (2-pyridyl)methyl, 2-(2-pyridyl)ethyl, 1-phenylethyl, $CH(CONH_2)CH_2C_6H_5$, $CH(CONH_2)CH_2CH(CH_3)_2$, $CH(CONH_2)CH(CH_3)CH_2CH_3$, and **R16** is H, methyl, ethyl, or 2-aminoethyl. N**R16R12** can optionally form an N-linked monocyclic or bicyclic heterocyclic ring, including but not limited to 1,2-dihydroisoindole, morpholine, piperidine, piperazine, N-alkyl piperazine (C1-C4), 3-pyrroline, pyrrolidine, or tetrahydroisoquinoline. **R4**, **R12** and **R16** are optionally further substituted, independently, with 1 to 3 of the following substitutents: OH, F, Cl, Br, methyl, CF_3, CF_3O, methoxy, alkylthio, $CONH_2$, $C(NH)NH_2$, $NHC(NH)NH_2$, N**R6R7** where **R6** and **R7** are H or alkyl and optionally form a ring. Unsubstituted carbons in aromatic rings are optionally substituted with N.

Molecular Design Considerations

The docking models of the MAPKK1 fragment and the In-2-LF inhibitor are used for the improvement of existing small molecule inhibitors and the de-novo design of new inhibitors. The resulting MD trajectory of the LF-MAPKK1 fragment complex is currently being used to provide the basis for the design of an improved *DynaPharm*®

pharmacophore template, which is a central part of a virtual library screening strategy for discovery and optimization of more potent inhibitors.

First, flexible and rigid regions on the surfaces of LF and MAPKK1 in the cleavage region of the complex model are being determined from the MD trajectory. Detailed analyses are being carried out at the surface of the N-terminal portion of MAPPK1 residing in the LF active site in order to extract characteristics of the interacting residues over the trajectory. Residues at the interface are identified and grouped using the following criteria: 1) contribution to the energetics of its binding to LF and 2) analysis of hydrophobicity. After grouping residues, the distances and angles between each residue in the group are measured and tabulated. Whenever aromatic or non-aromatic rings are involved, the centers of the rings are used for distance evaluation. For side chains longer than Alanine, the center of mass of the residue are used as the reference point for measuring the distances and angles. This will yield the desired virtual constructs of the residues (including dynamic motion) for constructing a *DynaPharm*® template and for more refined docking-based approaches.

The new docking models have been applied to a 1-hydroxyhydropyrazin-2-one scaffold identified previously. Computational docking studies on hydroxypyrazinones using the LF structure suggested that the ring hydroxamic acid group would be prevented from chelating zinc because of unfavorable steric interactions between ligand and protein.

However, these studies also suggested that derivatives of these structures tethered to other zinc-binding groups (such as carboxylic acid or thiol) could show activity. Figure C-3 shows a few examples of hydroxypyrazinones exhibiting activity in the Western Blot assay. Only structure SBI-031592, which contains an additional carboxylic acid moiety, showed activity in the FRET assay. The methyl ester of SBI-031592 was inactive in this assay, suggesting that the carboxylic acid moiety in itself is important for activity, while the hydroxamic acid groups in the pyrazinone ring are insignificant. Analogs of hydroxypyrazinones without hydroxyl groups (pyrazinones and alkoxypyrazinones) did not differ significantly from hydroxypyrazinones in the Western Blot assay, a result that is also inconsistent with a model involving zinc binding to the ring hydroxamic acid group in these compounds.

In light of these SAR results for hydroxypyrazinones and the computational predictions, attention was given to other scaffolds, including hydroxamic acids, carboxylic acids, thiols and barbituric acids. Computational docking studies and similarity searching helped to identify scaffolds related to SBI-031592, containing nitrogen heterocycles linked to 2 or 3 phenyl rings, and exemplified by scaffolds B, E, F, G, H, J and K in Figure C-4. Computational studies based on interactions of the MAPKK1 peptide with LF and further similarity searching helped to identify scaffolds A, C, and D. Based on both computational and assay data, scaffolds C and J in Figure C-4 were identified as of particular interest. Preliminary results suggest that some inhibitors with scaffold J exhibit selectivity against LF versus MMP-1 (IC_{50} (MMP-1)/ IC_{50} (LF) >6). Scaffold C is particularly interesting because of its relative potency and drug-like nature. The drug-like nature of scaffold C derives from the fact that one molecule in this class has been tested in mice as a candidate inhibitor of another target (TNF sheddase) and successfully prevented the lethal effects of lipopolysaccharide + galactosamine by blocking TNF synthesis (Mohler, K.M. *et al., Nature* **370**:218 (1994). The compound thus appears to be non-toxic in mice and sufficiently bioavailable and stable to reach the target enzyme. Derivatives of scaffold C will be examined in an effort to improve its potency.

Structures and measured IC_{50} values (FRET assay) for some of the hydroxamic acid derivatives are presented in Figure C-5. Note that three of the derivatives have single digit micromolar IC_{50} values and one has an IC_{50} value of 1.6μM. While more analog compounds are still being designed, synthesized and tested to gain a better understanding of structure/activity relationships, some preliminary conclusions can nevertheless be made. Scaffold B is an inhibitor, while its enantiomer is inactive, consistent with a specific interaction with LF near the binding site as opposed to nonspecific protein binding. For scaffold C, the most promising to date, the 2 fused aromatic rings (naphthyl and indole) and the alkyl group on the succinic diamide appear to contribute significantly to binding, while R3 is less critical. Intermediates for the synthesis of more than 40 other members of the C scaffold family have recently been prepared, using the docking model depicted in Figure C-6 as a guide.

Structures and measured IC_{50} values for some of the carboxylic acid derivatives examined to date are presented in Figure C-7. Three of these derivatives are active in the single digit μM range. For the carboxylic acid scaffold series G, although there is little dependence on chain length, n = 5 appears to be close to optimal. Competitive inhibition has been observed for individual compounds in the G and J scaffolds, consistent with binding near the active site. A docking model of a member of the J series bound to the LF active site is depicted in Figure C-6. Note that direct binding to zinc occurs for the hydroxamic acid moiety or the carboxylate moiety in both docking models shown in Figure C-6.

The X-ray crystal structure of LF has been computationally refined and combined with the AHM model of MAPKK1 to derive a full solvated MD trajectory of a bound LF-MAPKK2 fragment complex, and a bound complex of LF and the inhibitor In-2-LF. The bound complex models have been used to design and screen new scaffolds and derivatives of candidate LF inhibitors. Compounds with IC_{50} activities in the single digit micromolar range have been discovered for 3 novel scaffold families, with the most active to date being 1.6μM.

At that point where 100nM range compounds are identified, the co-crystallization task will be initiated for the most promising compounds, which will provide even more accurate structural information with which to further optimize the LF inhibitor candidates toward the 1 – 10nM activity goal.

Strategies for improving stability to enzymatic degradation will include amide replacement by C-C bond containing moieties or heterocycles, replacements of readily oxidized sites (e.g. replacement of phenyl by 4-fluorophenyl, 1-butyl by 2-fluoro-1-butyl). Strategies to minimize toxicity will include replacement of potentially toxophoric groups by less toxic bioisosteres (e.g. replace 3-nitrophenyl with 3-aminosulfonylphenyl or 3-acetylphenyl) and changes that improve selectivity for LF versus other metalloenzymes. Strategies to maximize selectivity against LF compared to other enzymes will include computationally guided alterations in the size of appropriate moieties. Using this same approach, extension of methyl groups to heptyl or benzhydryl has been used to increase the selectivity of certain hydroxamic acids between matrix

metalloprotease subtypes by >500 fold (Whittaker *et al.*, *Chem. Rev.* V. 99, 2735-2776 (1999); Miller *et al.*, *Bioorg. Med. Chem Lett* 7:193 (1997)). Strategies for improving bioavailability will include enhancing solubility by decreasing symmetry, introducing branching, reducing molecular weight, and substituting hydrophobic groups with polar groups such as alkoxy and aliphatic amines. Both solubility and membrane permeability are enhanced as needed by making substitutions that optimize log P and log D values, such as replacing arginine side chains with less polar 2-aminopyridines, replace amide CONH with $COCH_2$, thiazole, oxadiazole, oxazole, alkene, etc. Figure D-4 shows examples of how some of these strategies are applied, using the LF inhibitor scaffolds C and J as starting points. The structures of those more promising inhibitors are treated similarly as for scaffolds C and J in Figure D-4 using similar types of structural alterations and bioisosteric replacements.

Prodrug strategies are applied to agents that are predicted to show poor oral bioavailability, but are otherwise promising in terms of ADMET properties and potency when administered subcutaneously (s.c.) to mice. These will include strategies that have proven useful for other metalloproteinase inhibitors, e.g. ethyl esters as prodrugs of carboxylic acids and thioethers as prodrugs of thiols (Alton *et al.*, *J. Chromatogr* **579**:307-317 (1992); Noble *et al.*, *J Pharmacol Exp Ther* **261**:181-90 (1992); Skiles *et al.*, *Current Medicinal Chemistry* **8**:425-474 (2001)).

The basis for the substitutions proposed in analogs depicted in Figure D-4 is as follows (small letter designations in the list correspond to the letters in Figure D-4):

a) CH >> CF to improve metabolic stability.

b) Increased steric bulk within cavity to improve selectivity against LF versus other metalloenzymes.

c) CH >>N to optimize log D for bioavailability.

d) Decrease rotatable bonds through structural constraints for improved bioavailability.

e) α-alkylation enhances hydroxamic acid metabolic stability.

f) H>>CF_3 to adjust log D for bioavailability, and to improve metabolic stability.

g) Replace amide with heterocycle for improved metabolic stability, optimization of log D for bioavailability, decrease in NH bond count (Lipinski *et al.*, *Adv. Drug Del. Rev.* **23**:3-25 (1997)).

h) Replace amide with C-C for improved metabolic stability, optimize log D for bioavailability, decrease in NH bond count (Lipinski's rules). One example of significant improvement in oral bioavailability of a metalloprotease inhibitor through replacement of NH with CH_2 has been described by Chapman *et al. Bioorg. Med. Chem. Lett.* **6**:803 (1996) (Lipinski *et al.*, 1997).

j) Replace with alternate heterocycle for improved solubility and drug-like character.

k) CF_3>>OCH_3 for improved solubility, optimization of log D for bioavailability.

m) Eliminate phenyl group for improved solubility, optimization of log D for bioavailability, and lower molecular weight.

n) CF_3>>F for lower molecular weight.

p) Replace hydroxamic acid moiety with thiol for decreased mutagenicity; thioester prodrug for increased bioavailability.

q) Create acetoxymethyl ester of carboxylic acid as prodrug to improve oral bioavailability.

r) Append tertiary amine for improved solubility.

Inhibitor Compounds of the Invention

According to the design considerations and strategies described above, the compounds according to the following structural formula will find use as inhibitor compounds useful for treating anthrax infections by inhibiting Anthrax Lethal Factor (LF) activity. LF inhibitors are useful, either alone or together with other therapeutic compositions, in the prevention and treatment of anthrax infections, whether resulting from infection by *Bacillus anthracis* spp., or purposefully induced invasions by LF.

Synthesis of Inhibitor Compounds of the Invention

In general, the compounds of the present invention can be prepared in accordance with chemical synthetic protocols well known to those of skill in this art. One desirable category of such techniques is known by the generic term "combinatorial chemistry." Such techniques are well know in the art, and can be generally summarized as follows: For example, preparation of libraries can be by the "split synthesis" method, as described in Gallop *et al.*, *J. Med. Chem.*, **37**:1233-1251 (1994). The split synthesis procedure involves dividing a resin support into n equal fractions, in a separate reaction carry out a single reaction to each aliquot, and then thoroughly mixing all the resin particles together.

Repeating the protocol for a total of x cycles can produce a stochastic collection of up to n^x different compounds. An alternative format is by preparing sub-libraries in the $O_3O_2X_1$ format, wherein two positions on the compounds, O_3 and O_2 are explicitly defined and a third position, X_1, varies. Such sub-libraries can be conveniently prepared by the tea-bag technique, as is known in the art, and described, for example in U.S. Pat. No. 4,631,211 and Houghten *et al.*, *Proc. Natl. Acad. Sci.*, **82**:5131-5135 (1985).

Alternatively, or in addition thereto, the iterative selection and enhancement process of screening and sub-library resynthesis can be employed. For example, a sub-library of various R1 substituents can be screened to select the most active R1 substituent. The compound having the most active R1 is then resynthesized and with the R1 position being defined, a new R2 position mixture library is prepared, screened, and the most active R2 selected. The above process can then be repeated to identify the most active R substituents on the backbone structure.

In yet another approach, the positional scanning technique, only a single position is defined in a given sub-library and the most preferred substituent at each position of the compound is identified.

The advantage of synthetic combinatorial libraries (SCLs) made up of mixtures of tens of millions of different compounds is that they can be used to rapidly identify individual, active compounds without the need to individually synthesize, purify, and test every single compound. Since the libraries are in solution (i.e., not attached to a bead, pin, phage, glass, etc.) they can be screened in virtually any assay system.

Solution phase combinatorial chemistry methods can be used when the product can be separated from side products and starting materials through rapid techniques. Examples of these are: (1) selective precipitation of product and removal of byproducts and precursors by washing, (2) selective removal of side products and starting materials using chemically reactive polymers and/or ion exchange polymers ("scavenge"), (3) selective binding of product to a chemically reactive polymer, followed by removal of the product through a second chemical reaction ("capture") (4) selective binding of product to an ion exchange polymer, followed by removal with acid, base, or high salt buffer ("capture"), and (5) selective solubilization of product. Solution phase combinatorial

chemistry approaches are covered in a recent set of reviews (*Tetrahedron*, **54**:3955-4150 (1998)).

The synthetic approaches can be optimally carried out using solution phase combinatorial chemistry. Several reactions are carried out simultaneously using a multiple reaction vessel block such as, but not limited to, the Charybdis Calypso™ temperature controlled blocks, with gas manifolds to maintain an argon or nitrogen atmosphere. Alternately, the reactions can be carried out simultaneously in multiple vials filled with argon or nitrogen and fitted with magnetic stirbars and polytetrafluoroethylene-lined, sealed caps, by heating and stirring them simultaneously in a magnetic stirrer/heater such as, but not limited to, the Pierce ReactTherm™ III Heating/Stirring Module. The products are isolated by addition of water and filtration using a system such as, but not limited to, the Charybdis Calypso™ filtration block or polypropylene syringes fitted with filter disks made from polyethylene, polytetrafluoroethylene, or glass and attached to a vacuum manifold.

Representative synthetic schemes for some of the structures proposed in Figure D-4 are depicted in Figure D-5. Representative combinatorial libraries and their synthetic schemes are shown in Figure D-6. Individual compounds are synthesized using high-throughput methods and screened to determine synthetic feasibility and the activity of a representative structure. (High throughput procedures will include solid phase chemistry and solution phase chemistry with solid-phase reagents and scavengers. Where appropriate, microwave chemistry using Personal Chemistry Synthesizer instrumentation is carried out to increase the efficiency of library synthesis.) If the synthetic accessibility and potency are adequate, a virtual library (100-1000 structures) are constructed and added to the set of libraries to be used for the second round of *in silico* ADMET screening. After *in silico* screening has been used to remove structures that are unlikely to exhibit favorable ADMET profiles, the structures remaining in the virtual library are synthesized using high-throughput procedures.

For certain compounds of the present invention, synthesis can be readily accomplished by resort to the following general protocols:

The procedures in Schemes 1 through 4 can be used to make the subset of claimed structures in which:

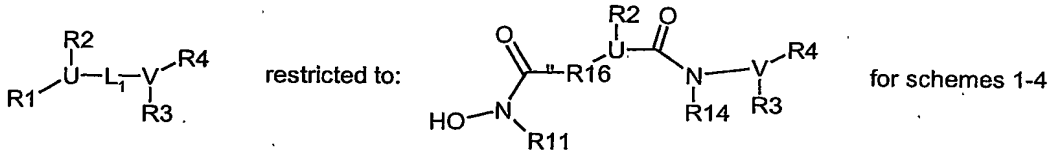
U is CH or C(CH3),

R1 is **R16Y** where

R16 is **Z**(CH**R5**)n, where n is 0 to 5, **Z** is a bond, **Y** is CON**R11**OH , **L1** is CONH or CON(**R14**) where **R14** is H or alkyl

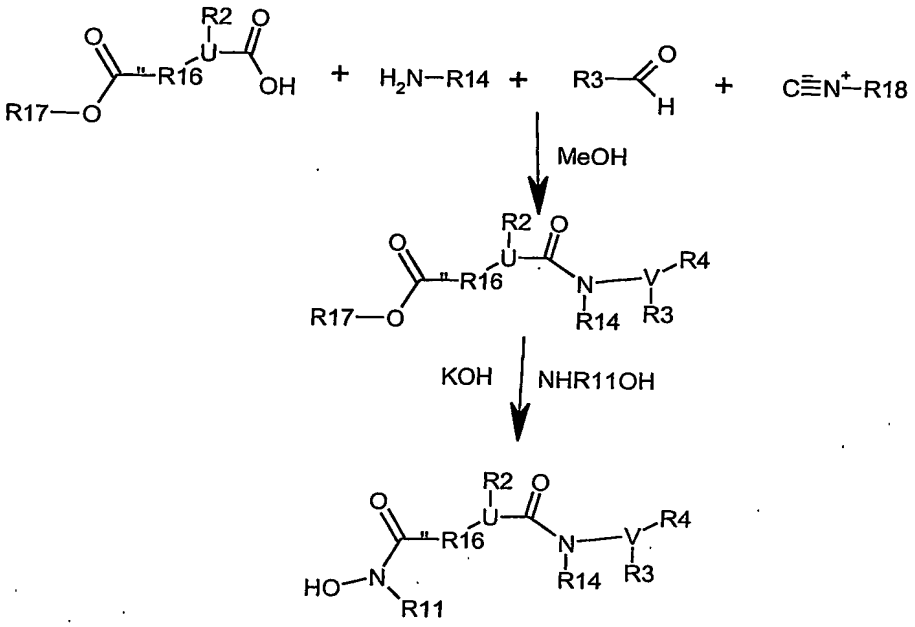
where **R15** is H or alkyl, and **R2, R3, R4, R5, R11** and **V** are as described previously in the more general embodiments.

The protocols also can be used for those structures in which **U, R5, Y** and **R11** form a ring, as described in the text and depicted in Figure B.



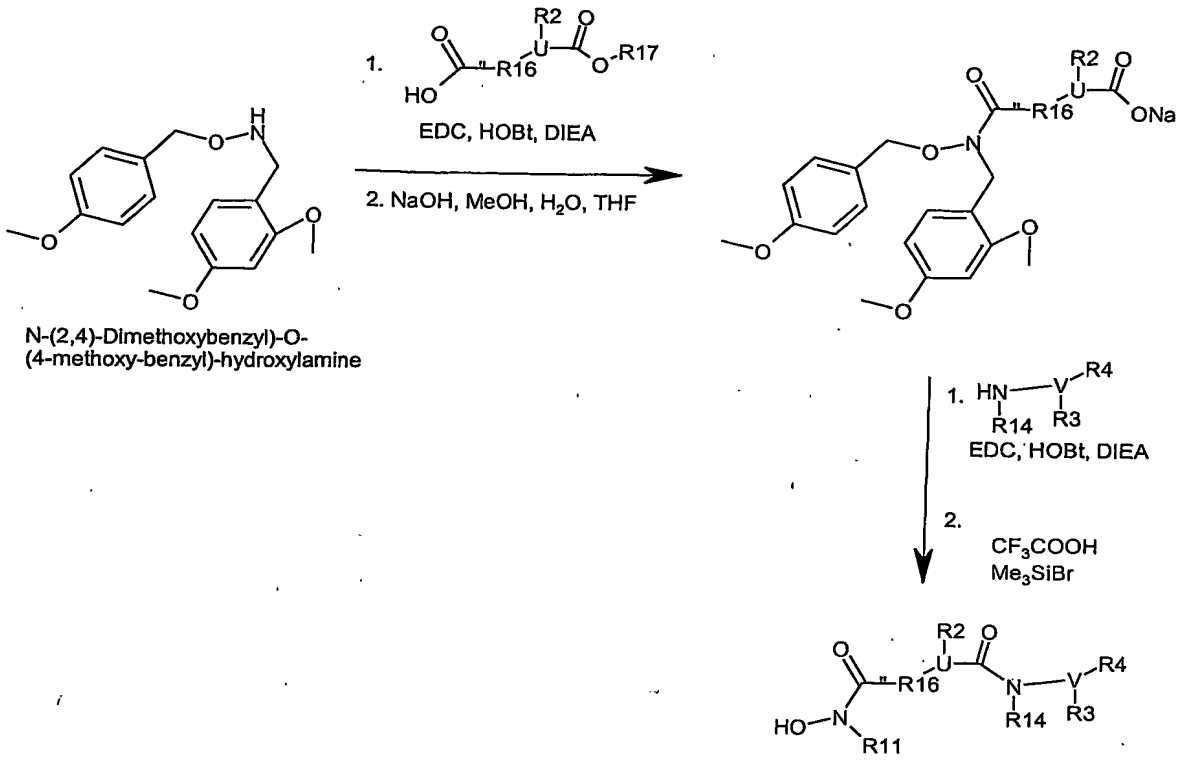
In the synthetic schemes shown here, if any of the Rn groups contain functionality that may interfere with or become chemically changed by the synthetic procedures shown, then these will be derivatized with appropriate, standard protecting groups that are not cleaved during the synthetic procedures, and which can be removed when needed without affecting other functionality.

Scheme 1



In Scheme1, the structure is further restricted such that **R17** is alkyl or benzyl, **R14** is H or primary alkyl, **R3** is a substituent linked through carbon (including Aryl, arylaryl, alkyl, arylalkyl, **R18** is alkyl, aryl, arylalkyl, **V** is CH, and **R4** is CONH**R18**.

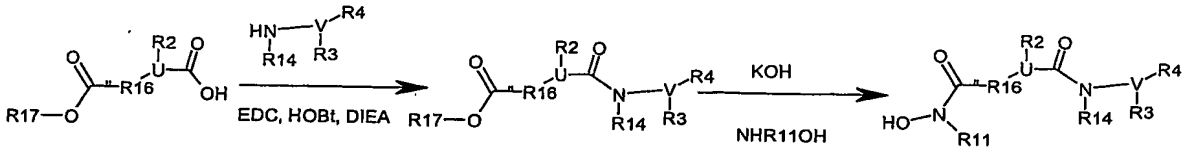
Scheme 2



In Scheme 2, the structure is further restricted such that **R11** is H.

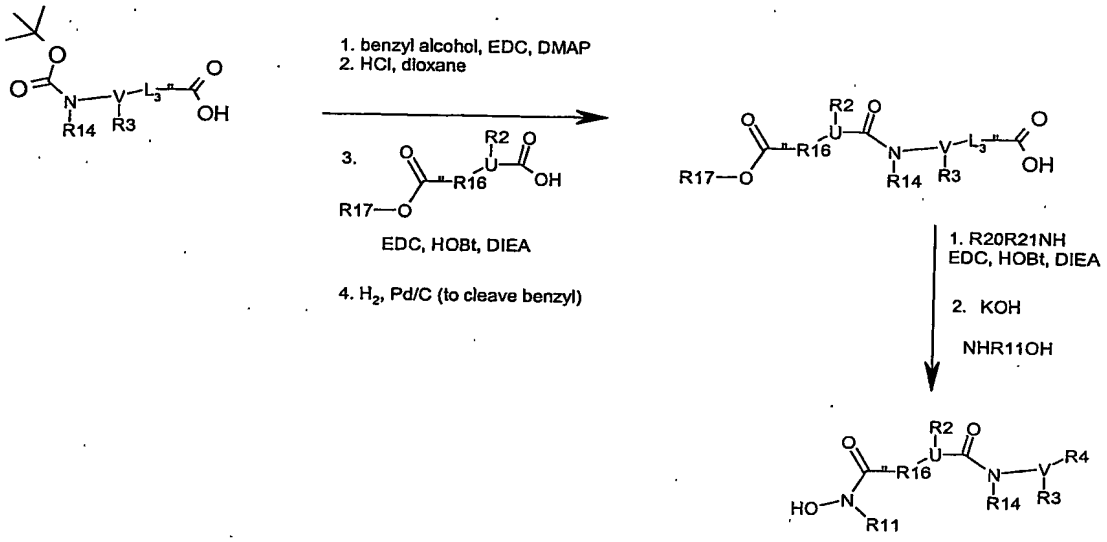
Synthesis of N-(2,4)-Dimethoxybenzyl)-O-(4-methoxy-benzyl)-hydroxylamine is detailed in Examples 10 and 11.

Scheme 3



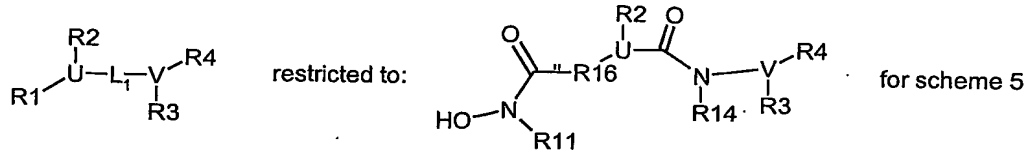
In Scheme 3, R17= methyl or ethyl.

Scheme 4

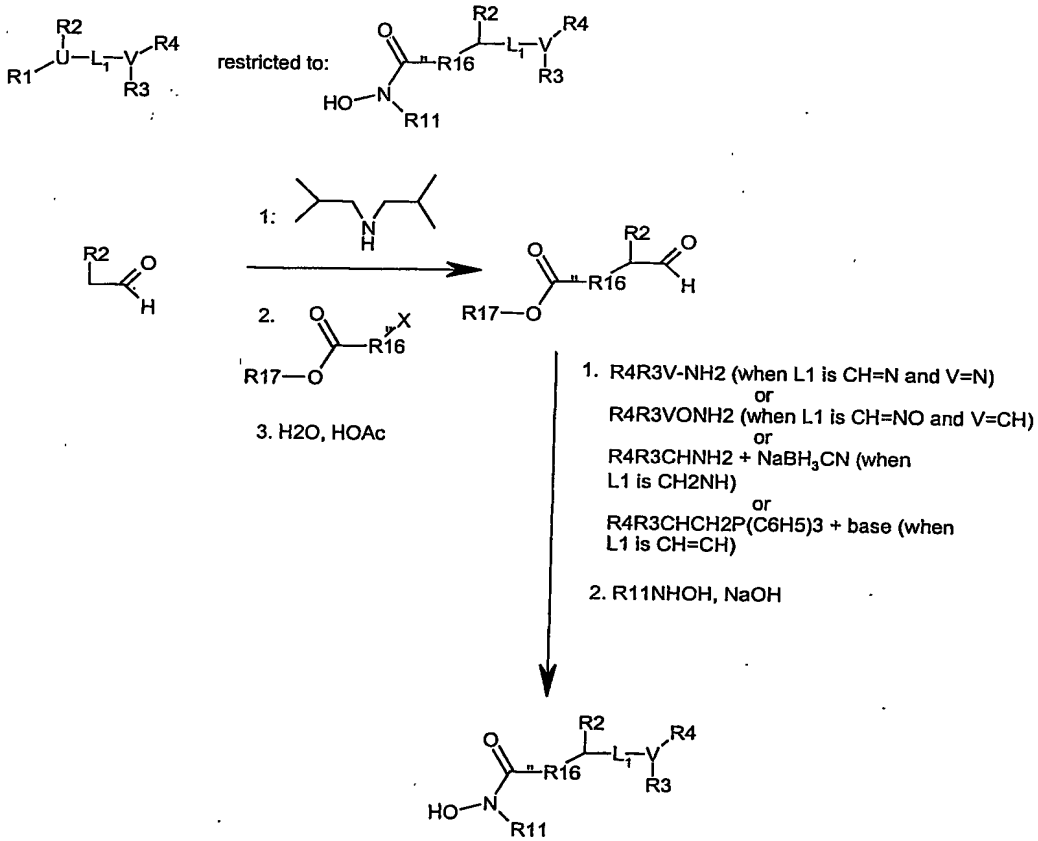


In scheme 4, the structures are further restricted such that **R11** is H, **R17** is methyl or ethyl, **R4** is **L3CONR20R21** in which **L3** is a bond, CH_2, CH_2CH_2, CH=CH, or cycloalkylidene (C3-C6), optionally further substituted with 1 or more alkyl, aryl, heteroaryl, heterocycloalkyl, OH, amine, or fluorine substituents, **R20** and **R21** are, independently, methyl, alkyl, benzyl, indanyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, optionally further subsituted with 1 or more alkyl, aryl, heteroaryl, alkoxy, carboxyl, heterocycloalkyl, OH, amine, or fluorine substituents.

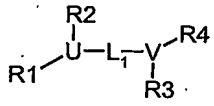
The procedures in Scheme 5 can be used to make the subset of claimed structures in which **U** is CH, **R1**is **R16Y** where **R16** is **Z**(CH**R5**)n, where **Z** is a bond, **Y** is CON**R11**OH, **L1** is CH=N, CH=NO, CH_2NH or CH=CH, **R17** is alkyl or benzyl, and **R2**, **R3**, **R4**, **R5**, **R11** and **V** are as described previously in the more general embodiments.



Scheme 5



In scheme 6, **R16** is **Z**(CH**R5**)n where where n is 0 to 4, **Z** is a bond, aromatic ring (1,2 or 1,3 or 1,4-linking), heteroaromatic ring 1,2 or 1,3 or 1,4-linking), **R2**=R11 is primary alkyl, arylalkyl,heteroarylalkyl, cycloalkylalkyl; **U** is N, **L1** is a single bond, **V** is C, where **V**, **R3** and **R4** form a 1,3,4-thiadiazole ring as shown above, **R5** and **Y** substituents are as described in the description of the more general embodiments, and **R12** is aryl, arylaryl, heteroarylaryl, aryloxyaryl, arylthioaryl, arylketoaryl, and heteroaryl analogs of these. **Z**, **R5**, **R2**, and **R12** are optionally further substituted with one or more trifluoromethyl, alkyl, alkoxy, hydroxy, carboxyl, amine, aminoalkyl, cycloalkyl, heteroaryl, or aryl groups. **Pro** is protecting group, e.g. ethyl (in ester) for carboxylic acid.



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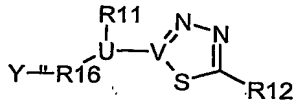
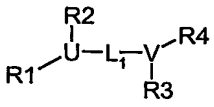


In scheme 7, **R16** is **Z**(CH**R5**)n where n is 0 to 4, **Z** is a bond, aromatic ring (1,2 or 1,3 or 1,4-linking), heteroaromatic ring 1,2 or 1,3 or 1,4-linking), **R2** is no substituent, **U** is N, **L1** is a double bond, **V** is C, where **U**, **V**, **R3** and **R4** form an amino-thiadiazoline ring as shown above, **R5** and **Y** substituents are as described in the description of the more general embodiments, and **R12** is aryl, arylaryl, heteroarylaryl, aryloxyaryl, arylthioaryl, arylketoaryl, and heteroaryl analogs of these. **Z**, **R5**, **R2**, and **R12** are optionally further substituted with one or more trifluoromethyl, alkyl, alkoxy, hydroxy, carboxyl, amine, aminoalkyl, cycloalkyl, heteroaryl, or aryl groups. **Pro** is a protecting group, e.g. ethyl (in ester) for carboxylic acid.



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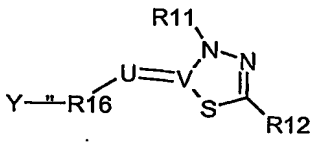
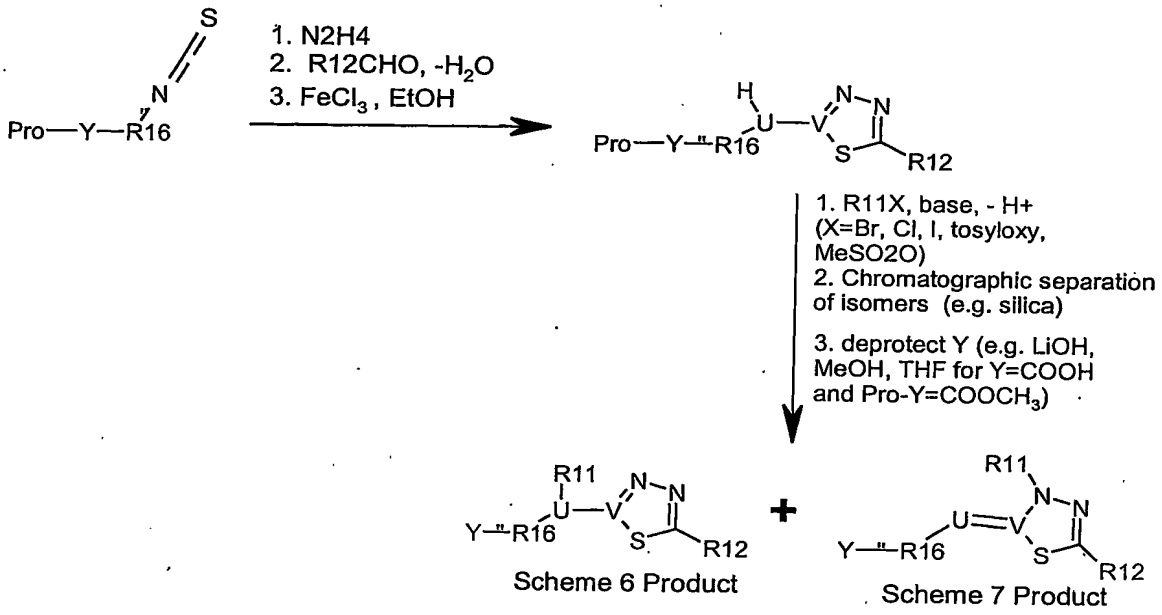
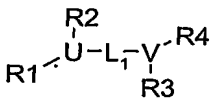


The products of schemes 6 and 7 are isomers made through identical routes, with separation of isomers before the final deprotection.

Schemes 6 and 7



In scheme 8, **R16** is **Z**(CH**R5**)n where where n is 0 to 4, **Z** is a bond, aromatic ring (1,2 or 1,3 or 1,4-linking), heteroaromatic ring 1,2 or 1,3 or 1,4-linking), **R2=R11** is primary alkyl, arylalkyl,heteroarylalkyl, cycloalkylalkyl; **U** is N, **L1** is a single bond, **V** is C, where **V**, **R3** and **R4** form a 1,3,4-thiadiazole ring as shown above, **Y** is C(**R20**)=NO(CH_2)mCOOH where **R20** is methyl, hydroxymethyl, alkyl, or cycloalkyl; m is 1 to 5; **R5** is as described in the description of the more general embodiments, and **R12** is aryl, arylaryl, heteroarylaryl, aryloxyaryl, arylthioaryl, arylketoaryl, and heteroaryl analogs of these. **Z**, **R5**, **R2**, **R20** and **R12** are optionally further substituted with one or more trifluoromethyl, alkyl, alkoxy, hydroxy, carboxyl, amine, aminoalkyl, cycloalkyl, heteroaryl, or aryl groups. **Pro** is a protecting group, e.g. ethyl (in ester) for carboxylic acid. **R17** is alkyl or benzyl.



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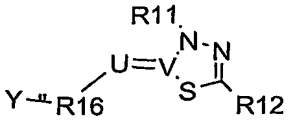
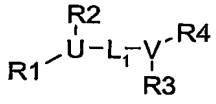


In scheme 9, **R16** is **Z**(CH**R5**)n where n is 0 to 4, **Z** is a bond, aromatic ring (1,2 or 1,3 or 1,4-linking), heteroaromatic ring 1,2 or 1,3 or 1,4-linking), **R2** is no substituent, **U** is N, **L1** is a double bond, **V** is C, where **U**, **V**, **R3** and **R4** form an imino-thiadiazoline ring as shown above, **Y** is C(**R20**)=NO(CH_2)mCOOH where **R20** is methyl, hydroxymethyl, alkyl, or cycloalkyl; m is 1 to 5; **R5** is as described in the more general embodiments, and **R12** is aryl, arylaryl, heteroarylaryl, aryloxyaryl, arylthioaryl, arylketoaryl, and heteroaryl analogs of these. **Z**, **R5**, **R2**, and **R12** are optionally further substituted with one or more trifluoromethyl, alkyl, alkoxy, hydroxy, carboxyl, amine, aminoalkyl, cycloalkyl, heteroaryl, or aryl groups. **Pro** is a protecting group, e.g. ethyl (in ester) for carboxylic acid. **R17** is alkyl or benzyl.



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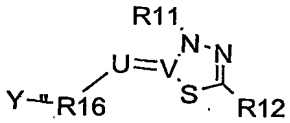
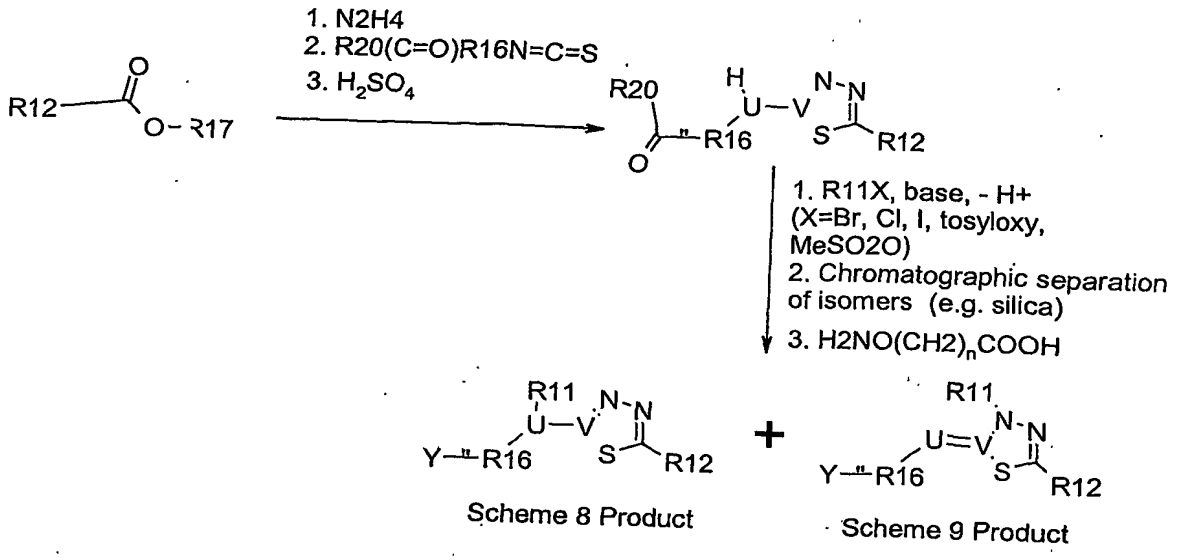


The products of schemes 8 and 9 are isomers made through identical routes, with seperation of isomers before the final deprotection.

Schemes 8 and 9



Other in vitro testing:

Other *in vitro* studies will be desirable for full assessment of candidate LF inhibitors. These studies, listed here for the sake of completeness, are: (1) LF inhibitory activity in vitro; (2) Efficacy against LT cytotoxicity in macrophages (external contract); (3) Ames test for mutagenicity (external contract - if the Ames test proves positive for compounds with otherwise favorable ADMET and activity profiles, more extensive genotoxicity and carcinogenicity studies in rats are carried out as needed); (4) set of PanLabs screens (external contract); and (5) cytotoxicity tests in human and rodent monocytic and hepatocyte cell lines (6) stability studies and (7) formulation.

Anthrax Lethal Factor FRET-based Enzymatic Assay

Materials:

Peptide Substrate [(Cou)Consensus(K(QSY-35)GG)-NH_2] (MW=2533): 1 mg/mL in Hepes buffer (395μM).
Lethal Factor Protease (MW=90,000): 1mg/mL (10μL/tube; 11μM).
Assay Buffer: 20mM Hepes, pH7.0, 1mM CaCl2, 0.1mg/mL BSA, 0.01% Tween-20.
Stop Solution: 4mM 1,10-phenanthroline/40mM EDTA.

Enzymatic Assay Protocol for compound screen:

To each well of a 96-well flat-bottomed black plate, add the following:

25μL of 12 μM peptide substrate in assay buffer (final conc. 4μM),
20μL: 1.5μL compounds in DMSO mixed with 18.5μL assay buffer,
30μL of 20nM of LF in assay buffer (final conc. 8nM)
Mixed well, and incubate at 25°C for 15 minutes
25μL of Stop Solution added to terminate the reaction.

The fluorescence was read on a Victor 1420 plate reader with the umbelliferone protocol (excitation 355 nm/emission 460 nm).

Background wells use reactions without enzyme.

Reference: Cummings et al., Proc. Natl. Acad. Sci., 99(10):6603-6 (2002)

Assay for Matrix Metalloproteinase-1 (MMP1)

1) Prepare the reaction buffer:	50mM HEPES pH 7.5 10mM $CaCl_2$ 0.01% Tween20 ± 0.01% BSA	2.5mL 0.5M HEPES pH 7.5 0.25mL 1.0M $CaCl_2$ 50μL 5% Tween 33μL 7.5% BSA Add H_2O to 25mL

2) Dilute the enzyme in reaction buffer to 15 units/μL (10μL of MMP1 stock to 1ml of reaction buffer) and distribute to 96-well plate 80μL/well
3) Dilute Substrate stock 20 x in the reaction buffer→ Add 20μL of substrate to Enzyme solution→ mix→ Incubate the plate @30°C for time course→ Read Umbiliferone protocol 360/460→ and process the data.

Enzyme-	Matrix Metalloproteinase-1 (MMP1, intestinal collagenase human, recombinant with C-terminal purification tag, E. coli expressed) catalytic domain 81-249aa, MW=19.9 kDa. Biomol #SE-180 11,547u/μg, total of 10μg in 19μL.
Substrate-	Fluorescent MMP Substrate, [DNP-PChaGCHAK(Nma)], MW= 1077.2, Biomol CATALOG NO: P-128, Km=10μM for MMP1, 1mg of net peptide/vial diluted in 1mL of DMSO as 1mM, store @ -20°C. Protocol 360/460nm

Plates-	Corning#3656 96well Non-binding surface black plates

Note:
Preparing Enzyme Stock (150units/μL): original MMP1 stock (0.53μg/μL, or 6120units/μL) dilute 1μL into 41μL of Enzyme buffer→ aliquot 10μL/tube (150units/μL, 76 tubes total)→ Store the tubes @ -70°C.

MMP1 Enzyme Buffer-	50mM Tris-HCl pH 7.5	0.5mL 1M stock
	5mM $CaCl_2$	0.05mL 1M $CaCl_2$
	300mM NaCl	0.6mL 5M NaCl
	20μM $ZnCl_2$	0.02mL 10mM $ZnCl_2$
	0.5% Brij35	0.5mL 10% Brij35
	30% Glycerol	3mL 100% Glycerol
		Add H_2O to 10mL

Preparing of Substrate Stock (20mM in DMSO)- 1mg solid dissolved in 50μL of DMSO→ Store @ -20°C

Preclinical Toxicity And Efficacy Studies In Mice using LT Challenge

In this task, approximately 20 compounds are chosen, on the basis of the best overall performance in the set of *in vitro* ADMET screens in Task 2, for further evaluation in live animals using Lethal Toxin (LT) challenge (LT is the toxic combination of LF and the permeabilizing factor, PA). The goal is for this set of compounds to consist of at least 2 representatives of each structural subclass.

Mouse studies described in this section (acute toxicity studies and efficacy studies involving LT-injected mice) are carried out in female mice, A/J strain, 6 weeks of age, weighing approximately 20g each. The strain, gender and age were chosen based on a mean lifespan when exposed to 4 x LD50 of anthrax LT that is sufficiently long (mean 3.7 days) to allow the possibility of post-toxin treatment as well as prophylaxis (Welkos *et al.*, *Infection and Immunity* **51**:795-800 (1986)). This 3.7-day lifespan is also similar to the mean lifespan (3 days) of mice infected with 5000cfu of *bacillus anthracis* spores. The planned trials, and associated schedules and protocols are presented in the following sub-sections.

Acute toxicity in mice

Single doses of drug candidates are injected s.c. into sets of 5 mice per dose level using 0.1, 0.3, 1, 3, and 10mg/kg. Animals are observed for 14 days to estimate the MTD or to determine the lower limit of the MTD (the highest dose at which no more than 10% of the mice show clear signs of toxicity). Mice are weighed daily and their food consumption measured. For this preliminary study, the signs of toxicity are limited to nausea, lethargy, anorexia, weight loss, abnormal fur texture, diarrhea or mortality within the 14-day observation period. Mice showing signs of pain due to toxic effects are euthanized immediately. Combination toxicity studies of each candidate at its MTD with ciprofloxacin will also be carried out, because compounds that exhibit significant adverse interactions with ciprofloxacin are not worthy of further consideration. Compounds must have maximum tolerated doses above 1mg s.c. for further consideration (the dose used for inhibition of the TACE metalloprotease by the compound). For mice with an MTD > 1mg/kg, postmortem gross necropsy is carried out on 5 mice from the

group with the highest tolerated concentration on day 14. If no toxicity is observed at 10mg/kg, the dose is increased until the maximum tolerated dose is determined (~ 10% incidence of clear toxicity).

Prophylactic Efficacy against LT in mice (mortality endpoint)

Initially, efficacy studies involving single injections of LT and single s.c. doses of drug candidate are carried out to eliminate molecules that have insufficient efficacy for further study. For each experiment 10 mice (control group) are injected s.c. with 0.3mL saline, and 10 (treated group) s.c. with drug candidate in 0.3mL saline, to be administered 5 minutes prior to the LT injection. All 20 animals will then be injected with 50μg of PA combined with 10μg of LF (4 x LD50). Surviving mice are observed for 14 days for signs of LT-induced nonlethal toxicity.

Prophylactic Efficacy against LT in mice (MEK-1 cleavage endpoint)

Related experiments will use the ratio of LF-cleaved to uncleaved MEK-1 in macrophages as an endpoint. Because it is difficult to isolate sufficient numbers of monocytes from peripheral blood in mice, uninduced peritoneal macrophages are used. For each experiment 10 mice (control group) are injected s.c. with 0.3mL saline, and 10 (treated group) s.c. with drug candidate in 0.3mL saline, to be administered 5 minutes prior to an i.p. LT injection. At $t = 2$ hours after injection, mice are sacrificed and peritoneal macrophage isolated by flushing the peritoneal cavity with 4mL of 0.34 M sterile-filtered sucrose.. Each mouse is expected to yield roughly 3×10^6 macrophages (Lefkovits and Benvenuto, Immunological Methods, Vol II, Academic Press, New York, p.291 (1981). The suspension is immediately combined with an equal volume of 2% sodium octadecylsulfate containing 2mM EDTA and 2mM phenanthroline in order to lyse the macrophages and stop LF activity. The ratio of cleaved to uncleaved MEK-1 is determined using Western Blot analysis with a specific anti-MEK-1 monoclonal antibody. Based on the kinetics of MEK cleavage in macrophages and the rapid activity of lethal toxin rodents, 2 hours of exposure to LT should be sufficient time for

measurable MEK cleavage to occur in macrophages (Tonello *et al.*, *Nature* **418**:386 (2002), Fish *et al.*, *J. Infect. Dis.* **118**:114-124 (1968); Welkos *et al.*, (1986)). Western Blot analysis should be sufficient for determining the cleaved to uncleaved MEK-1 ratio because it has been used to determine inhibition of LF activity inside live culture macrophage cell lines (Tonello *et al.*, 2002), and 20ng of MEK-1 (cleaved + uncleaved) has been found more than sufficient for quantitation using this technique.

Usually, drug candidates that cause > 4-fold increase in lifespan relative to controls and a statistically significant (P>0.95) decrease in the cleaved/ uncleaved MEK-1 ratio in the prophylactic studies are carried forward. Approximately 12 such molecules are chosen for further studies.

Efficacy against LT in mice at t = 1 hour post injection:

The 12 candidates that meet criteria outlined in the prophylaxis study with MEK-1 cleavage endpoint will undergo a study in mice in which the candidates are administered at **t** = 1 hour, 2 hours, and 3 hours after injection using 10 control mice and 20 treated mice. (Sets of 20 treated mice are used for each candidate and dose schedule to allow statistical significance even if 50% of the treated mice die before the **t** = 3 hour injection time). Surviving mice from treated groups are observed for 14 days after the first injection of LF + PA.

Only drug candidates that increase lifespan at least 2-fold relative to controls (with statistical significance, P> 0.95) are considered for the oral prophylaxis studies. However, compounds with very strong prophylactic activity will also be included for further study in the live challenge experiments, even if they are not very active in the therapeutic efficacy study, because the LT concentrations are well below 4 x LD_{50} until a very late stage of the infection. Approximately 8 compounds are chosen for the next step.

Oral prophylaxis in LT-treated mice:

Compounds active in the mortality endpoint prophylaxis study with adequate PK are tested for oral prophylaxis in mice. "Adequate oral PK" is defined as >40% oral

bioavailability and a serum half-life > 2.5 hours. Both oral and s.c. PK are determined for the compounds on a contract basis by Cerep, Inc., enabling calculation of the serum half-life and % oral bioavailability.

Approximately 6 compounds are chosen for oral activity studies in mice, based on their optimal performance in the oral PK studies. The procedure for these studies is very similar to the s.c. studies in the prophylaxis study with a mortality endpoint: for each experiment 10 mice (control group) are treated p.o. with 0.1mL vehicle, and 10 mice (treated group) s.c. with a selected drug candidate in 0.1mL vehicle, to be administered **t** minutes prior to the LT injection. The value of **t** will be such that the time between agent administration (oral gavage) and LT injection will be longer so that the mean peak concentration of agent in plasma corresponds with the time of LT injection (based on the oral PK data). All 20 animals will then be injected with 50μg of PA combined with 10μg of LF ($4 \times LD_{50}$). Surviving mice are observed for 14 days for signs of LT-induced nonlethal toxicity.

Long-term non-GLP toxicity studies:

Six of the most promising candidates, chosen based on the mouse and rat efficacy, acute toxicology and PK studies, will undergo extensive, long-term, non-GLP toxicity studies in mice, with complete blood workup and postmortem organ histopathology based on a multiple s.c. injection schedule (2x daily for 5 days) suitable for live bacillus anthracis experiments. To the extent possible, the candidate compounds are chosen to represent a variety of structural subclasses. The maximum tolerated dose at this schedule will be determined in this way.

The following Examples serve to illustrate certain preferred embodiments and aspects of the present invention and are not to be construed as limiting the scope thereof. The structures of various of the disclosed compounds will be found depicted in Figure 1.

Experimental

In the experimental disclosure which follows, all weights are given in grams (g), milligrams (mg), micrograms (μg), nanograms (ng), or picograms (pg), all amounts are given in moles, millimoles (mmol), micromoles (μmol), nanomoles (nmol), picomoles (pmol), or femtomoles (fmol), all concentrations are given as percent by volume (%), proportion by volume (v:v), molar (M), millimolar (mM), micromolar (μM), nanomolar (nM), picomolar (pM), femtomolar (fM), or normal (N), all volumes are given in liters (L), milliliters (mL), or microliters (μL), and linear measurements are given in millimeters (mm), or nanometers (nm) unless otherwise indicated.

The following Examples demonstrate the practice of the present invention in synthesizing compounds according to the invention, generally as depicted in Figure 1, and in methods by which drugs having the formulas shown can be readily identified by routine assay procedures to demonstrate that they possess the desired activity.

Example 1: Methyl (3R)-3-(N-{[N-(tert-butyl)carbamoyl](3-phenylphenyl)methyl} carbamoyl)-5-methylhexanoate

In an ice bath under dry conditions, added 2M NH_3/CH_3OH (1mL). A solution of 3-phenylbenzaldehyde (0.14g, 0.77mmol) in 2mL MeOH was added to the mixture and stirred for 5 min in cold and 10 min at room temperature. Added 2-aza-3,3-dimethylbut-1-ene (0.064g, 0.77mmol) and (2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoic acid (0.145g, 0.77mmol) in 3mL MeOH to the mixture and refluxed (80-85°C) for overnight. The title product precipitated out and was collected by filtration, washing with MeOH and hexanes and drying in vacuo to yield 0.068g of the desired compound (20% yield). MS $(M+H)^+$:453.

Example 2: Compound 1: Methyl (3R)-3-(N-{[N-(tert-butyl)carbamoyl](3-phenylphenyl)methyl}carbamoyl)-5-methylhexanoate

KOH (1.60g, 28.5mmol) was dissolved in dry MeOH(8mL). NH_2OH-HCl (1.251g, mmol) was dissolved in dry MeOH (12mL) and cooled to 0°C. The KOH solution was poured into the NH_2OH-HCl solution and stirred for 1 hour. The product from Example

1 (67mg, 0.148mmol) was dissolved in dry MeOH (0.3mL). The KOH/ NH_2OH-HCl solution (1.19mL) was filtered into this solution and stirred for 1-2 hours at room temperature. Reaction completion was detected by LC/MS. The reaction mixture was concentrated in the removal of MeOH. The residue was dissolved in H_2O (3mL) and acidified to pH = 6 with 6N HCl, and neutralized with saturated $NaHCO_3$ (pH = 9). The product precipitated and was collected by filtration. Purification of the product was either done by recrystallization or C18 silica gel reverse phase chromatography (filter funnel) with water/methanol mixtures, yielding the title product (0.051g) in 76% yield (diastereoisomeric mixture of 23/77 ratio), R_f= 0.72 (ethyl acetate/methanol, 9 : 1). MS $(M-H)^-$ 452.

Example 3: (2S)-N-((1S)-1-carbamoyl-2-methylpropyl)-2-[(tert-butoxy) carbonylamino]-3-naphthylpropanamide

A solution of (S)-N-Boc-1-Naphthylalanine (630mg, 2mmol), L-valineamide hydrochloride (306mg, 2mmol), 1-hydroxybenzotriazole (306mg, 2mmol) in dichloromethane was treated with EDC HCl (768mg, 4mmol) and diisopropylethylamine (1.216mL, 7mmol) and the mixture was stirred overnight. The dichloromethane was rotovaped, the residue was taken in ethylacetate. The ethylacetate solution was washed with 1N HCl (2 x 10mL), saturated sodiumbicarbonate solution (2 x 10mL) and finally with brine (2 x 10mL). The ethylacetate solution was dried over anhydrous sodium sulphate and rotovaped. The residue on trituration with hexanes gave a whit solid. Yield: 625mg. (75%). MS $(M+Na)^+$:436

Example 4: Synthesis of (2S)-N-((1S)-1-carbamoyl-2-methylpropyl)-2-amino-3-aphthylpropanamide, chloride

(2S)-N-((1S)-1-carbamoyl-2-methylpropyl)-2-amino-3-aphthylpropanamide, chloride was prepared by treating product from Example 3 (0.62g, 1.5mmol) with 4N HCl/Dioxane for 30 minutes. The dioxane was rotovaped and the residue was triturated with ether and dried under vacuum. Yield: 0.48g. (93%). This was used without further purification.

Example 5: phenylmethyl (4S)-4-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-4-[(tert-butoxy) carbonyl amino] butanoate

Phenylmethyl (4S)-4-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-4-[(tert-butoxy) carbonyl amino] butanoate was prepared using the procedure in Example 3 from Boc-L-Glu(Obzl)-OH (3.37g 10mmol), L-leucinamide (1.43g, 11mmol), EDC HCl (3.84g, 20mmol), anhydrous hydroxy benzotriazole (1.35g, 10mmol) and diisopropylethylamine (3.48mL, 20mmol). Yield: 3.8g (88%).
MS ($M+H^+$-Boc Group) 350.

Example 6: (4S)-4-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-4-[(tert-butoxy) carbonylamino]butanoic acid

(4S)-4-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]- 4-[(tert-butoxy) carbonylamino]butanoic acid was prepared by dissolving the product from Example 5 (3.6g, 8mmol) in a mixture of MeOH (20mL), THF (5mL) and 1N sodiumhydroxide (20mL). The mixture was stirred until the TLC shows the absence of starting material. Methanol and THF were rotovaped, the residue was diluted with water and washed with ethylacetate (2 x 20mL). The aqueous layer was cooled in ice bath and acidified with 1N hydrochloric acid to pH of 3. Now the compound was extracted with ethylacetate (3 x 50mL). The combined ethylacetate extracts were washed with brine (2 x 10mL) and dried over anhydrous sodium sulphate and ethylacetate was rotovaped. The residue on trituration gave a white solid. Yield 2.7g (96%).

^{1}H NMR: (300 MHz, $CDCl_3$): 12.09 δ (1H bs); 7.71 δ (1H d); 7.30 δ (1H d); 7.10 δ (2H dm); 4.24 δ (1H m) 3.88 δ (1H m); 1.84 δ (6H m); 1.43 δ (10H m); 0.94 δ (6H m).

Example 7: (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(tert-butoxy) carbonylamino]-N'-[2-(4-phenylphenyl)ethyl]pentane-1,5-diamide:

A solution of (4S)-4-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-4-[(tert-butoxy) carbonylamino] butanoic acid (1.08g, 3mmol) in DMF (20mL) was treated with 2-(4-phenyl phenyl)ethylamine (0.985g, 5mmol) anhydrous hydroxyl benzotriazole (0.405g,

3mmol), 1-[3-Dimethyl amino)propyl]-3-ethylcarbodiimide hydrochloride (1.152g, 6mmol) and diisopropyl- ethylamine (1.04mL, 6mmol). The mixture was stirred for overnight at room temperature. Next day, DMF was rotovaped under reduced pressure and the residue was taken in ethylacetate. The ethylacetate was washed with 1N HCl (2 x 15mL), Saturated sodium carbonate (2 x 15mL) and brine (2 x 15mL), and ethylacetate layer was dried over anhydrous sodium sulphate and rotovaped. The rersidue on triturating with hexane gave a solid. Yield: 1.2g (74%).

^{1}H NMR: (300 MHz, DMSO-d6): 7.91 δ (1H t); 7.73 δ (1H d); 7.65 δ (5H m); 7.46 δ (2H m); 7.30 δ (4H m) 7.01 δ (1H d); 4.26 δ (1H m); 3.86 δ (1H m); 3.87 δ (2H m); 2.75 δ (2H t); 2.50 δ (2H m); 1.50 δ (5H m); 1.38 δ (9H s); 0.84 δ (6H m).

Example 8: (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-N'-[2-(4-phenylphenyl)ethyl]pentane-1,5-diamide, chloride

(2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-N'-[2-(4-phenylphenyl)ethyl] pentane-1,5-diamide, chloride was prepared by treating (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(tert-butoxy)carbonylamino]-N'-[2-(4-phenylphenyl)ethyl]pentane-1,5-diamide (1.08g, 2mmol) with 4N HCl in dry dioxane (10mL). The mixture was stirred for 30 minutes, the dioxane was rotovaped, and the residue was triturated with ether and dried under vacuum. Yield: 0.87g (91%). This material used without further purification.

Example 9: 2,4-Dimethoxy benzaldehyde oxime

2,4-Dimethoxy Benzaldehyde (8.3g, 50mmol) was dissolved in 150mL of Hydroxylamine hydrochloride (4.1g, 60mmol) and 15mL of pyridine were added and the mixture was stirred at ambient temperature for one hour. The solution was diluted with 250mL of water and extracted with ethyl acetete(150mL, 3 times). The organic extracts were dried over magnesium sulfate, concentrated on the rotary evaporator and excess pyridine was removed on the high vacuum pump to afford 9g (~99%) of the title compound as a white solid.

^{1}HNMR ($CDCl_3$, 300MHz) δ 10.9 (s,1H), 8.15 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 6.53 (m, 2H), 3.77 (s, 3H), 3.75 (s, 3H). LS/MS C9H11NO3 calculated for: ($M+H^+$) 182, found: 182.

Example 10: 1-{(1E)-2-aza-2-[(4-methoxyphenyl)methoxy]vinyl}-2,4-dimethoxybenzene

Method 10A: 2,4-Dimethoxy benzaldehyde oxime (3.6g, 20mmol, see Example 9), 4-methoxy Benzyl chloride (3.4g, 22mmol) , and tetra-butyl ammonium iodide (1.1g, 3mmol) were dissolved in 200mL of THF and cooled to 0°C by an ice bath. Sodium Hydride (1.1g, 26mmol, 60% dispersion) was added in 4 portions to the stirring mixture. The ice bath was removed and the reaction was stirred for 2 hours and when the starting oxime had been completely consumed (as judged by tlc analysis) the reaction was quenched by the addition of 200mL of saturated ammonium chloride. The aqueous phase was extracted three times with 15mL of ethyl acetate. The combined organics were dried over magnesium sulfate, concentrated on the rotary evaporator and subjected to silica gel chromatography (hexanes: ethyl acetate; 6/4). The title compound, 5.4g, was isolated in 90% yield.

^{1}HNMR ($CDCl_3$, 300MHz) δ 8.22 (s,1H), 7.53 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.54 (m, 2H), 4.99 (s, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.70 (s, 3H). LS/MS C17H19NO4 calculated for: ($M+H^+$)302, found: 302.

Method 10B: Under dry conditions, 2,4-dimethoxybenzaldehyde (4.3g, 26mmol) and [(4-methoxyphenyl)methyl]oxyamine hydrochloride (5g, 26mmol) were stirred in dichloroethane (90mL) for 10 min. Added sodium triacetoxyborohydride (8.3g, 39mmol) and stirred for overnight. Quenched with sodium hydrogen carbonate (saturated) until pH = 8. Extracted with ethyl acetate. Ethyl acetate was dried over sodium sulfate, filtered, and concentrated give the title compound in 69% yield. MS $(M+H)^+$:302.

Example 11: N-(2,4-Dimethoxy-benzyl)-O-(4-methoxy-benzyl)-hydroxylamine

2,4-Dimethoxy-benzaldehyde O-(4-methoxy-benzyl)-oxime (5.4g, 18mmol, see Example 10) was dissolve in methanol and sodium cyanoborohydride (60mmol) was added. The reaction mixture was stirred and concentrated HCl was added dropwise until the pH was maintained ~ 3. The reaction was stirred for 2 hours maintaining the pH below 3 by adding additional HCl as necessary. The solution was carefully neutralized with saturated sodium hydrogen carbonate and the amine was extracted with ethyl acetate (150mL, three times). The combined organics were dried over sodium sulfate and concentrated on the rotary evaporator. The crude amine was purified on silica gel (hexanes:ethyl acetate; 2/8) to provide 4.9g (90%) of the title compound as an amorphous white solid, Mp 52-55°C(ethyl acetate/hexanes).

^{1}HNMR (DMSO, 300MHz) δ 7.28 (d, J = 9.0 Hz, 2H), 7.13 (d, J = 9.0 Hz, 1H), 6.87 (d, J = 9.0 Hz, 2H), 6.43 (m, 2H), 4.64 (s, 2H), 3.99 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H). LS/MS C17H21NO4 calculated for: ($M+H^+$) 304, found: 304.

Example 12: Methyl (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy]carbamoyl} methyl)-4-methylpentanoate

Methyl (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy] carbamoyl} methyl)-4-methylpentanoate was prepared using the procedure in Example 7 from (R)-2-Isobutyl succinic acid 1-methyl ester (1.0g, 5.3mmol), [(2,4-dimethoxy phenyl)methyl][(4-methoxyphenyl)methoxy]amine (1.82g, 6mmol), EDC HCl (2.03g 10.6mmol), anhydrous hydroxyl benzotriazole (0.735g, 5.3mmol), Diisopropylethylamine (1.84mL, 10.6mmol) and methylenechloride (30mL). Yield: 1.8g (76%). MS ($M+H^+$) 474.

Example 13: (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl) methoxy]carbamoyl}methyl)-4-methylpentanoic acid, sodium salt

(2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy] carbamoyl}methyl)-4-methylpentanoic acid, sodium salt was prepared from Methyl (2R)-

2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy] carbamoyl} methyl)-4-methylpentanoate (1.51g, 3.2mmol) using the procedure similar to Example 6. After completion of the reaction, the reaction mixture was cooled in ice bath and the neutralized with 1N HCl to pH = 7 and then basified with sodium bicarbonate solution. The mixture was purified using a short column of RP-C-18 silica gel, and eluted with 30% Methanol in water. Yield: 0.95g (57%). MS ($M-H^+$) = 458.

Example 14: 2-[(2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl) methoxy]carbamoyl}methyl)-4-methylpentanoylamino](2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-N'-[2-(4-phenylphenyl)ethyl]pentane-1,5-diamide:

2-[(2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy] carbamoyl}methyl)-4-methylpentanoylamino](2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-N'-[2-(4-phenyl phenyl)ethyl]pentane-1,5-diamide was prepared from (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-N'-[2-(4-phenylphenyl)ethyl] pentane-1,5-diamide (285mg, 0.6mmol), Methyl (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl) methoxy] carbamoyl} methyl)-4-methylpentanoate (240mg, 0.5mmol), EDC HCl (192mg, 1mmol), anhydrous hydroxybenzotriazole (68mg, 0.5mmol), diisopropylethylamine (191μL, 1.1mmol), and DMF (4mL) using the procedure as in Example 7. Yield: 395mg (88%).

^{1}H NMR: (300 MHz, $CDCl_3$): 8.42 δ (1H bs); 7.78 δ (1H d); 7.40 δ (12H m); 6.86 δ (2H d); 6.42 δ (2H m) 6.08 δ (1H b); 5.26 δ (1H m); 4.73 δ (4H m); 4.20 δ (1H m) 3.76 δ (9H m); 3.67 δ (2H b); 2.80 δ (4H m); 2.62 δ (1H dm); 2.37 δ (2H m) 3.17 δ (1H m); 1.68 δ (6H m); 1.38 δ (2H m); 0.94 δ (6H m).

Example 15: Synthesis of Compound 2: {2-[2-(N-hydroxycarbamoylmethyl)(2R)-4-methylpentanoylamino](2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-N'-[2-(4-phenylphenyl)ethyl]pentane-1,5-diamide}

The product from Example 14 (0.3g, 0.34mmoles) was treated with a 4/1 (v/v) mixture of trifluoroacetic acid and trimethylsilyl bromide under drying tube and the mixture was stirred for two hours. The solvent was rotovaped, the residue was triturated with

ethylacetate and the residue was put on a short column of RP C-18 silica gel and eluted with a mixture of water and methanol, increasing the methanol concentration from zero to 80%. The compound was eluted in 80%. Yield 25mg (12.5%).

^{1}H NMR: (300 MHz, DMSO-d6): 10.46 δ (1H s); 8.80 δ (1H s); 8.16 δ (1H d); 7.92 δ (1H t); 7.63 δ (5H m) 7.48 δ (2H t); 7.34 δ (4H m); 7.00 δ (1H s); 4.20 δ (2H m); 3.30 δ (2H t); 2.74 δ (3H t); 2.16 δ (6H m); 1.56 δ (5H s); 0.90 δ (12H m).

Example 16: 3-Formyl-heptanoic acid ethyl ester

Hexanal (5g, 50mmol) and diisobutyl amine (6.5g, 50mmol) were dissolved in 200mL of benzene and refluxed for 8 hours under a Dean Stark apparatus. The solution was cooled to room temperature and bromo ethyl acetate (12.5g, 75mmol) was added and the reaction was refluxed for 20 hours. The reaction was cooled to room temperature and 20mL of a 3/1 (water/acetic acid) solution was added and the mixture was heating under reflux for two hours. The mixture was cooled diluted with saturated sodium carbonate and the organic layer was collected. The aqueous layer was extracted two times with ether. The combined organics were dried over sodium sulfate, filtered and concentrated on the rotary evaporator. The crude residue was purified on silica gel (Ethyl acetate/hexane: 5/95) to afford 7g of the title compound (75%).

^{1}HNMR ($CDCl_3$, 300MHz) δ 9.75 (s, 1H), 4.17 (q, J = 6.9 Hz, 2H), 2.86-2.70 (m, 2H), 2.43 (dd, J = 5.1, 5.1 Hz, 1H), 1.78-1.27 (m, 9H), 0.94 (t, J = 6.3 Hz, 3H).

Example 17: Compound 3: (3-(Benzyloximino-methyl)-heptanoic acid hydroxyamide)

3-Formyl-heptanoic acid ethyl ester (300mg, 1.7mmol) and O-Benzyl hydroxylamine hydrochloride (270mg, 1.7mmol) were dissolved in THF. Pyridine (268mg, 3.4mmol) was added and the mixture was stirred for 30 minutes. The reaction was diluted with saturated ammonium chloride and extracted three times with 50mL of ethyl acetate. The combined organics were dried over sodium sulfate, filtered and concentrated on the rotary

evaporator. The residue was purified on silica gel (ethyl acetate/hexanes; 3/7) to give 150mg of 3-(Benzyloxyimino-methyl)-heptanoic acid ethyl ester (30%). 3-(Benzyloxyimino-methyl)-heptanoic acid ethyl ester (150mg, 0.49mmol) was converted to the title compound using the procedure in Example 2 (hydroxyl amine hydrochloride/KOH in dry methanol) to yield 72mg (53%) of Compound 3. LC/MS $C_{15}H_{22}N_2O_3$, calculated for ($M-H^-$): 277, found: 277.

Example 18: Compound 4: {2-(Hydroxycarbamoylmethyl-amino)-4-methyl-pentanoic acid [1-(1-carbamoyl-ethylcarbamoyl)-2-naphthalen-2-yl-ethyl]-amide}

2-Amino-propionamide (L isomer) (1.2g, 9.5mmol) and 2-tert-butoxycarbony-(L)-amino-3-naphthalen-2-yl-propionic acid (3g, 9.5mmol were coupled using the procedure in Example 3. The compound was isolated, after aqueous wash, by crystallization to afford 2.9g (79%)of (t-Butoxycarbonyl-L-naphthylalanyl-L-alanine) amide. The BOC group was removed by treatment with 50% TFA in dichloromethane for 30 minutes. The solvent was removed on the rotary evaporator and the product was dissolved in toluene and the toluene removed on the rotary evaporator, this was repeated three times. The TFA salt (7.5mmol) was taken up in dichloromethane, cooled to 0°C, and neutralized with triethylamine to yield (L-naphthylalanyl-L-alanine) amide. The free amine was coupled to N-(t-butoxycarbonyl)-L-leucine (1.8g, 7.5mmol) using the procedure in Example 3 to yield {N-(t-butoxycarbonyl)-L-leucylL-naphthylalanyl-L-alanine}amide. This tripeptide was deprotected with 50% TFA in dichloromethane and neutralized as previously described for afford 2.2g of 2-Amino-4-methyl-pentanoic acid [1-(1-carbamoyl-ethylcarbamoyl)-2-naphthalen-2-yl-ethyl]-amide (88%).

2-Amino-4-methyl-pentanoic acid [1-(1-carbamoyl-ethylcarbamoyl)-2-naphthalen-2-yl-ethyl]-amide (100mg, 0.25mmol) was dissolved in DMF, triethylamine (30mg, 0.3mmol) and N-Benzyloxy-2-bromo-acetamide (75mg, 0.3mmol) was added and the mixture was stirred for 72 hours at 50°C. The reaction mixture was diluted with ethyl acetate and washed with saturated ammonium chloride (aq). The organic layers were dried over sodium sulfate and concentrated on the rotary evaporator. The crude residue was purified

on silica gel (70% ethyl acetate in hexanes) to yield 90mg of 2-[(Benzyloxycarbamoyl-methyl)-amino]-4-methyl-pentanoic acid [1-(1-carbamoyl-ethylcarbamoyl)-2-naphthalen-2-yl-ethyl]-amide (65%).

The benzyl group was removed by palladium-catalyzed hydrogenolysis (10% Pd/C) in ethanol. The palladium was removed by filtration through a plug of celite. The ethanol was removed on the rotary evaporator on the title compound was re-crystalized from hot methanol to yield 55mg of Compound 4 as a white solid (71%). Mp = 205-212°C (methanol) Ms: $C_{24}H_{33}N_5O_5$ calculated for $(M+H^+)$:472, found: 472.

Example 19: (tert-butoxy)-N-indan-2-ylcarboxamide

In an ice bath, indane-2-ylamine (1.94mL,15mmol) and then added dioxane (20mL), 1M NaOH (30mmol), and tert-butyl (tert-butoxycarbonyloxy)formate (4.9g, 22.5mmol) respectively. After 1hour, the pH was adjusted to 9, and stirred overnight. The product precipitated out and was collected by filtration using 1N HCl (20mL), H_2O (20mL), and Hexanes to the isolation of the title compound (3.34g) in 95% yield.

^{1}H NMR (300MHz,d_6-DMSO): δ 7.147 (5H,m), 4.180 (1H, m), 3.089 (2H, q), 2.75 (2H,q), 1.390 (9H,s).

Example 20: (tert-butoxy)-N-indan-2-yl-N-methylcarboxamide

Under dry conditions, the product from Example 19 (3.14g, 13.4mmol) was stirred in DMF (20mL). NaH (0.339g, 10.1mmol) was added to the solution and stirred for 30 min. Iodomethane (2mL, 20.1mmol) was added to the mixture and stirred for overnight. DMF was removed by rotavap and high vacuum. The residue was extracted with EtOAc and washed with NaCl (aq). EtOAc was dried over Na_2SO4, filtered, and concentrated to the isolation of the title product (1.2g) in 36% yield. MS $(M-57+H)^+$ 192.

Example 21: Compound 5: 2-(N-hydroxycarbamoylmethyl)(2R)-N-[(N-indan-2-yl-N-methylcarbamoyl)(4-phenylphenyl)methyl]-4-methylpentanamide

2-[(tert-butoxy)carbonylamino]-2-(4-phenylphenyl)acetic acid (9.8g, 30mmol) and phenylmethan-1-ol (4.67mL, 45mmol) in 100mL of methylene chloride was added NMM (6.58mL, 60mmol), then EDC (11.52g, 60mmol) and DMAP (732mg, 6mmol) at 0°C. The reaction mixture was stirred at room temperature for overnight. The methylene chloride was evaporated (rotavap) under vacuum. The crude residue went through acid base work up to yield 13.62g (73%) of phenylmethyl 2-[(tert-butoxy)carbonylamino]-2-(4-phenylphenyl)acetate as a white solid. MS $(M+H\text{-}Boc)^+$ 318.

The removal of t-Boc of phenylmethyl 2-[(tert-butoxy)carbonylamino]-2-(4-phenylphenyl)acetate (13.58g, 32.5mmol)and 4N HCl in Dioxane (60mL) to yield 10.6g (92%) of phenylmethyl 2-amino-2-(4-phenylphenyl)acetate hydrochloride as white solid. MS $(M+H)^+$ 318.

Using the procedure of Example 3, phenylmethyl 2-amino-2-(4-phenylphenyl)acetate hydrochloride (9.4g, 26.5mmol), (2R)-2-(hydroperoxycarbonylmethyl)-4-methylpentanoic acid (5g, 26.5mmol), EDC (10.2g, 53mmol), HOBt (4g, 26.5mmol), NMM instead of DIEA (8.7mL, 79.5mmol) and dichloromethane (50mL) to yield 11.4g (88%) of methyl (3R)-5-methyl-3-(N-{[benzyloxycarbonyl](4-phenylphenyl)methyl} carbamoyl)hexanoate as a light yellow solid. MS $(M+H)^+$ 488.

The removal of the benzyl group from the benzyl ester was done by using methyl (3R)-5-methyl-3-(N-{[benzyloxycarbonyl](4-phenylphenyl) methyl} carbamoyl) hexanoate (6g, 12.3mmol), 10% palladium on carbon (600mg, 10% of ester), dry tetrahydrofuran (10mL), methanol (150mL) to yield 4.75g (97%) of 2-{(2R)-2-[(methoxycarbonyl) methyl]-4-methylpentanoylamino}-2-(4-phenylphenyl)acetic acid as a white solid. MS $(M+H)^+$ 398.

Using the procedure of Example 3, Indan-2-ylmethylamine hydrochloride (694mg, 3.77mmol), 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}-2-(4-phenylphenyl)acetic acid (1.5g, 3.77mmol), EDC (2.17g, 11.31mmol), HOBt (577mg,

3.77mmol), NMM instead of DIEA (1.65mL,15.08mmol) and dichloromethane (50mL) to yield 250mg (13%) of methyl (3R)-3-{N-[(N-indan-2-yl-N-methylcarbamoyl)(4-phenylphenyl) methyl] carbamoyl}-5-methylhexanoate as a yellow liquid.
MS $(M+H)^+$ 527.

Using the procedure of Example 2, KOH (1.6g,28.5mmol) was dissolved in dry MeOH (8mL). NH_2OH-HCl (1.25g, 18mmol) was dissolved in dry MeOH (12mL) and cooled to 0°C. The KOH solution was poured into the NH_2OH-HCl solution and stirred for 1hour. Methyl (3R)-3-{N-[(N-indan-2-yl-N-methylcarbamoyl)(4-phenylphenyl) methyl] carbamoyl}-5-methylhexanoateas (246mg, 0.46mmol) was dissolved in dry MeOH (0.94mL). The KOH/ NH_2OH-HCl solution (3.74mL) was filtered into the solution of Methyl (3R)-3-{N-[(N-indan-2-yl-N-methylcarbamoyl)(4-phenylphenyl) methyl] carbamoyl}-5-methylhexanoate and stirred for 1-2 hours at room temperature. Reaction completion was detected by LCMS. The reaction mixture was concentrated in the removal of MeOH. The residue was dissolved in H_2O (3mL) and acidified to pH = 6 with 6N HCl, and neutralized with saturated $NaHCO_3$ (pH = 9). The product precipitated and was collected by filtration. The crude product was purified by silica gel chromatography (water/methanol, 30:70) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-[(N-indan-2-yl-N-methylcarbamoyl)(4-phenylphenyl)methyl]-4-methylpentanamide (0.03g) in 13% yield (diastereoisomeric mixture of 23/77 ratio).
R_f= 0.65 (ethyl acetate/methanol, 4:1).

^{1}H NMR 1:1 Mixture (300MHz,d_6-DMSO): δ 10.394 (1H,s), 8.714 (2H,m), 7.499 (9H,m), 7.157 (4H,m), 6.078 (0.5H,m), 5.85 (0.5H,m), 5.36 (0.5H,m), 4.965 (0.5H,m), 2.839 (8H,m) 2.148 (2H,m), 1.369 (2H,m), 0.835 (6H,m).

Example 22: [4-(3,4-dichlorophenyl)phenyl]methylamine

In a 10mL glass tube were placed (4-bromophenyl)methylamine (0.186g, 1.0mmol), 3,4-dichlorophenylboronic acid (0.191g, 1.0mmol), bis(triphenylphosphine)palladium (II) chloride (0.035g, 0.05mmol), 1M Na_2CO_3 (2mL), CH_3CN (2mL) and a magnetic stir bar.

The vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation was used, and the reaction mixture was keep at 150°C for 250 seconds. After the mixture was allowed to cool to room temperature, the reaction vessel was opened and the contents were concentrated under vacuum. The crude solid residue was washed by water, hexanes, and dried under vacuum to give 0.158g (62%) of [4-(3,4-dichlorophenyl)phenyl]methylamine as yellow solid. MS $(M+H)^+$ 252, 254.

Example 23: 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid

To a solution of di-tert-butyl 2-(ethoxycabonylmethyl)malonate (15.10g, 49.9mmol) in 50mL of dry DMF was added sodium hydride (1.998g, 49.9mmol) at room temperature under an nitrogen atmosphere. When evolution of hydrogen ceased, the 1-iodo-2-methylpropane (11.57mL, 99.9mmol) was added, and the mixture was stirred for overnight at 65°C. The DMF was evaporated under vacuum. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), concentrated, and purified by flash chromatography (ethyl acetate / hexanes, 100% hexanes to 1:30) to give the light yellow oil of the tert-butyl ethyl 2-[(tert-butyl)oxycarbonyl]-2-(2-methylpropyl)butane-1,4-dioate (14.60g) in 82% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.12 (2H, q), 2.94 (2H, s), 1.90 (2H, d), 1.57-1.49 (1H, m), 1.45 (18H, s), 1.24 (3H, t), 0.89 (6H, d).

tert-Butyl ethyl 2-[(tert-butyl)oxycarbonyl]-2-(2-methylpropyl)butane-1,4-dioate (13.60g, 37.9mmol) in 50mL of TFA was stirred at room temperature for 2 hours. After TFA was removed to leave 9.33g of 2-[(ethoxycarbonyl)methyl]-2-(2-methylpropyl)propanedioic acid as dark yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.28 (2H, br s), 4.15 (2H, q), 3.13 (2H, s), 1.90 (2H, d), 1.77-1.68 (1H, m), 1.25 (3H, t), 0.93 (6H, d).

The 2-[(ethoxycarbonyl)methyl]-2-(2-methylpropyl)propanedioic acid (9.33g, 37.9mmol) was heated in the kugelrohr oven at 150-155°C for 20 minutes. When evolution of carbon dioxide ceased, the residue yellow oil was the 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid (6.05g, 79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.01 (1H, br s), 4.14 (2H, q), 2.95-2.90 (1H, m), 2.68 (1H, dd), 2.44 (1H, dd), 1.68-1.59 (2H, m), 1.34-1.27 (1H, m), 1.25 (3H, t), 1.00-0.90 (6H, m).

Example 24: Compound 6: N1-(3',4'-Dichloro-biphenyl-4-ylmethyl)-N4-(hydroxyl)-2-isobutyl-succinamide

To the product from Example 22 (0.125g, 0.49mmoles) and the product from Example 23 (0.100g, 0.49mmoles) in 5mL of methylene chloride was added HOBt (0.067g, 0.49mmol), followed by NMM (0.11mL, 0.99mmol), then EDC (0.190g, 0.49mmol) at 0°C. The reaction mixture was stirred overnight at room temperature under nitrogen. The methylene chloride was evaporated (rotavap) under vacuum. The crude residue was purified by flash chromatography (ethyl acetate / hexanes, 100% hexanes to 1:4) to give 0.130g (61%) of ethyl 3-(N-{[4-(3,4-dichlorophenyl)phenyl]methyl}carbamoyl)-5-methylhexanoate as colorless oil. MS $(M+H)^+$ 436, 438.

KOH (1.60g, 28.5mmol) was dissolved in dry MeOH (8mL). NH_2OH-HCl (1.251g, 18.0mmol) was dissolved in dry MeOH (12mL) and cooled to 0°C. The KOH solution was poured into the NH_2OH-HCl solution and stirred for 1 hour at 0°C. The ethyl 3-(N-{[4-(3,4-dichlorophenyl)phenyl]methyl}carbamoyl)-5-methylhexanoate (0.096mg, 0.22mmol) was dissolved in dry MeOH (0.44mL). The KOH/ NH_2OH-HCl solution (1.76mL) was filtered into this solution and stirred for 1h at room temperature. Reaction completion was detected by LC/MS. The reaction mixture was concentrated in the removal of MeOH. The residue was dissolved in H_2O (3mL) and acidified to pH = 6 with 1N HCl, and neutralized with saturated $NaHCO_3$ (pH = 9). The product precipitated and

was collected by filtration. Purification of the product was done by recrystallization from 2-propanol, yielding the title product (0.08g) in 86% yield. MS $(M-H)^-$ 421, 423.

Example 25: 2-bromo-1-(2,3,4,5,6-pentafluorophenoxy)ethane

In a 10mL glass tube were placed 2-(2,3,4,5,6-pentafluorophenoxy)ethan-1-ol (0.250g, 1.1mmol), NBS (0.215g, 1.2mmol), triphenylphosphine (0.316g, 1.2mmol), 4mL of CH_3CN and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation was used, and the reaction mixture was keep at 125°C for 700 seconds. After the mixture was allowed to cool to room temperature, the reaction vessel was opened and the contents were concentrated under vacuum. The crude residue was purified by flash chromatography (ethyl acetate / hexanes, 100% hexanes to 1:4) to give 0.330g (99%) of 2-bromo-1-(2,3,4,5,6-pentafluorophenoxy)ethane as colorless oil.

^1H NMR (300 MHz, $CDCl_3$): δ 4.45 (2H, t), 3.62 (2H, t).

Example 26: Compound 7: 3-(1-Methylcarbamoyl-2-naphthalen-2-yl-ethylcarbamoyl)-5-pentafluorophenyloxy-pentanoic acid:

2-[(ethoxycarbonyl)methyl]-4-(2,3,4,5,6-pentafluorophenoxy)butanoic acid: The title compound was prepared using the procedure for Example 23 from 2-bromo-1-(2,3,4,5,6-pentahluorophenoxy)ethane (2.00g, 6.9mmol), di-tert-butyl 2-(ethoxycabonylmethyl) malonate (2.08g, 6.9mmol) and sodium hydride (0.275g, 6.9mmol). Yield: 1.65g (70%).

^1H NMR (300 MHz, $CDCl_3$): δ 4.26 (2H, t), 4.16 (2H, q), 3.19 (1H, m), 2.80 (1H, dd), 2.63 (1H, dd), 2.22 (1H, m), 2.06 (1H, m), 1.26 (3H, t).

To a solution of 2-[(ethoxycarbonyl)methyl]-4-(2,3,4,5,6-pentafluorophenoxy)butanoic acid (0.132g, 0.37mmol) and (2S)-2-amino-N-methyl-3-(2-naphthyl)propanamide hydrochloride (0.098g, 0.37mmol) in 5mL of methylene chloride was added HOBt (0.050g, 0.37mmol), followed by NMM (0.122mL, 1.11mmol), then EDC (0.142g,

0.74mmol) at 0°C. The reaction mixture was stirred at room temperature under nitrogen for overnight. The methylene chloride was evaporated (rotavap) under vacuum. The crude residue was purified by flash chromatography (ethyl acetate / hexanes, 100% hexanes to 2:1) to give 0.170g (81%) of ethyl 3-{N-[(1S)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl]carbamoyl}-5-(2,3,4,5,6-pentafluorophenoxy)pentanoate as white solid. MS $(M+H)^+$ 567.

To a solution of ethyl 3-{N-[(1S)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl] carbamoyl}-5-(2,3,4,5,6-pentafluorophenoxy)pentanoate (0.170g, 0.30mmol) in 10mL of THF was added 20mL of 0.25M LiOH solution (in MeOH/H_2O, 75/25). The mixture was stirred 2 hours at room temperature and concentrated in vacuo. The residue added water, then added 1*N* HCl aq. solution until pH < 7. The solid was collected by filter and washed by water, then dried under vacuum give 0.160g (99%) of 3-{N-[(1S)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl]carbamoyl}-5-(2,3,4,5,6-pentafluorophenoxy) pentanoic acid as white solid. mp. 68-69°C; MS $(M+H)^+$ 539; $(M-H)^-$ 537.

Example 27: Compound 8: N4-Hydroxy-N1-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-2-(2-pentafluorophenyloxy -ethyl)-succinamide

To a solution of Compound 7 (0.122g, 0.23mmol, see Example 26) and 2H-3,4,5,6-tetrahydropyran-2-yloxyamine (0.027g, 0.23mmol) in 5mL of methylene chloride was added HOBt (0.031g, 0.23mmol), followed by NMM (0.0.05mL, 0.45mmol), then EDC (0.087g, 0.45mmol) at 0°C. The reaction mixture was stirred at room temperature under nitrogen for overnight. The methylene chloride was evaporated (rotavap) under vacuum. The residue was diluted with water and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N HCl (2 x 15mL), saturated sodium bicarbonate (2 x 15mL) and brine (15mL), and dried over anhydrous sodium sulphate and rotovaped.to give 0.130g (89%) of N'-(2H-3,4,5,6-tetrahydropyran-2-yloxy)-N-[(1S)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl]-2-[2-(2,3,4,5,6-pentafluorophenoxy)ethyl]butane-1,4-diamide as white solid. MS $(M-H)^-$ 636.

A mixture of N'-(2H-3,4,5,6-tetrahydropyran-2-yloxy)-N-[(1S)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl]-2-[2-(2,3,4,5,6-pentafluorophenoxy)ethyl]butane-1,4-diamide (0.130g, 0.2mmol) and PTSA (0.060g) in dry methanol (35mL) was stirred at room temperature for overnight. Then added 0.25 M LiOH solution until pH > 7. The methanol was evaporated, and the residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The crude residue was purified by C-18 flash chromatography (H_2O / MeOH, 100% H_2O to 2:8) to give 0.076g (69%) of 2-(N-hydroxycarbamoylmethyl)-N-[(1S)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl]-4-(2,3,4,5,6-pentafluorophenoxy)butanamide as white solid. MS $(M+H)^+$ 554; $(M-H)^-$ 552.

Example 28: Methyl (3R)-5-methyl-3-(N-{(9-methylcarbazol-3-yl)[N-benzylcarbamoyl]methyl}carbamoyl)hexanoate

In a 10mL glass tube were placed (9-methylcarbazol-3-yl)formaldehyde (0.209g, 1.0mmol), 2M solution of ammonia in methanol (1mL, 2.0mmol), benzyl isocyanide (0.122mL, 1mmol), (2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoic acid (0.188g, 1mmol), CH_3OH (4mL) and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation was used, and the reaction mixture was keep at 140°C for 2400 seconds. After the mixture was allowed to cool to room temperature, the reaction vessel was opened and the contents were concentrated under vacuum. The crude residue was purified by flash chromatography (ethyl acetate / hexanes, 100% hexanes to 1:2) to give 0.126g (25%) of methyl (3R)-5-methyl-3-(N-{(9-methylcarbazol-3-yl)[N-benzylcarbamoyl]methyl}carbamoyl)hexanoate.
MS $(M+H)^+$ 514.

Example 29: Compound 9: 2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-{(9-methylcarbazol-3-yl)[N-benzylcarbamoyl]methyl}pentanamide

KOH (1.60g, 28.5mmol) was dissolved in dry MeOH (8mL). NH_2OH-HCl (1.251g, 18.0mmol) was dissolved in dry MeOH (12mL) and cooled to 0°C. The KOH solution was poured into the NH_2OH-HCl solution and stirred for 1 hour at 0°C. The methyl (3R)-5-methyl-3-(N-{(9-methylcarbazol-3-yl)[N-benzylcarbamoyl]methyl}carbamoyl)

hexanoate (0.126mg, 0.24mmol) was dissolved in dry MeOH (0.49mL). The KOH/ NH_2OH-HCl solution (1.96mL) was filtered into this solution and stirred for 2 hours at room temperature. Reaction completion was detected by LC/MS. The reaction mixture was concentrated in the removal of MeOH. The residue was dissolved in H_2O (3mL) and acidified to pH = 6 with 1N HCl, and neutralized with saturated $NaHCO_3$ (pH = 9). The product precipitated and was collected by filtration. The crude product was purified by C-18 flash chromatography (H_2O / MeOH, 100% H_2O to 3:7) to give 0.100g (81%) of 2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-{(9-methylcarbazol-3-yl)[N-benzylcarbamoyl]methyl}pentanamide. MS $(M+H)^+$ 515; $(M-H)^-$ 513.

Example 30: Compound 10: Trans-2-(N-{-1-[N-(-1-carbamoylpropyl)carbamoyl]-2-naphthylethyl}carbamoyl)cyclohexanecarboxylic acid

(2S)-N-((1S)-1-carbamoylpropyl)-2-[(tert-butoxy)carbonylamino]-3-naphthylpropan amide was prepared by treating (S)-N-Boc-1-naphthylalanine (630mg, 2mmol), and S-2-aminobutyramide (204mg, 2mmol) with EDC HCl (576mg, 3mmol), anhydrous 1-hydroxybenzotriazole (306mg, 2mmol) and Diisopropylethylamide (522µL, 3mmol) in DMF. The mixture was subjected to microwave heating in Personal Chemistry microwave synthesizer at 160°C for 500 seconds. The solvent DMF was rotovaped under vacuum and the residue was taken in EtOAc and washed with 1N HCl (2 x 15mL), saturated sodiumbicarbonate solution (2 x 15mL) and brine (2 x 15mL). The EtOAc solution was dried over anhydrous sodium sulphate and rotovaped. The residue on trituration with hexane gave a solid. Yield: 635mg (79%). MS $(M+H)^+$ 400; $(M-45)^-$ 444.

(2S)-N-((1S)-1-carbamoylpropyl)-2-amino-3-naphthyl propanamide was prepared by treating (2S)-N-((1S)-1-carbamoylpropyl)-2-[(tert-butoxy)carbonylamino]-3-naphthylpropanamide (798mg, 2mmol) with 4N HCl in Dioxane (10mL) and the mixture was stirred for 30 minutes. The Dioxane was rotovaped, the residue was triturated with ether and then suspended in EtOAc and washed with saturated sodium carbonate solution and then with brine. The EtOAc solution was dried over anhydrous sodium sulphate and

rotovaped to get a solid. Yield: 300mg (50%). This material was used without further purification.

(2S)-N-((1S)-1-carbamoylpropyl)-2-amino-3-naphthyl propanamide

A mixture of (2S)-N-((1S)-1-carbamoylpropyl)-2-amino-3-naphthyl propanamide (0.46g) and trans-1,2-cyclohexanedicarboxylic anhydride (0.45g) in dichloromethane were stirred overnight. The solvent was rotovaped, the residual solid was washed with ethylacetate and filtered. Yield: 0.49g (72%).

^{1}H NMR: (300 MHz, DMSO-d6): 11.97 δ (1H d); 8.80 δ (1H s); 8.16 δ (1H d); 7.92 δ (1H t); 7.63 δ (5H m) 7.48 δ (2H t); 7.34 δ (4H m); 7.00 δ (1H s); 4.20 δ (2H m); 3.30 δ (2H t); 2.74 δ (3H t); 2.16 δ (6H m); 1.56 δ (5H s); 0.90 δ (12H m).

A mixture of (2S)-N-((1S)-1-carbamoylpropyl)-2-amino-3-naphthyl propanamide (0.46g) and trans-1,2-cyclohexanedicarboxylic anhydride (0.45g) in dichloromethane were stirred overnight. The solvent was rotovaped, the residual solid was washed with ethylacetate and filtered. Yield: 0.49g (72%).

^{1}H NMR: (300 MHz, DMSO-d6): 11.97 δ (1H d); 8.80 δ (1H s); 8.16 δ (1H d); 7.92 δ (1H t); 7.63 δ (5H m) 7.48 δ (2H t); 7.34 δ (4H m); 7.00 δ (1H s); 4.20 δ (2H m); 3.30 δ (2H t); 2.74 δ (3H t); 2.16 δ (6H m); 1.56 δ (5H s); 0.90 δ (12H m).

Example 31: Ethyl 3-[(hydrazinothioxomethyl)amino]benzoate

Hydrazine hydrate (0.51mL, 10.4mmol) was dissolved in 20mL of ethanol. This solution was stirred at 0°C and ethyl 3-isothiocyanatobenzoate (1.800g, 8.7mmol) was added dropwise. After complete addition ethyl 3-isothiocyanatobenzoate, the reaction mixture was warmed up to room temperature stirred for 2 hours. After being cooled to 0°C, the mixture was filtered and the solid washed by cold ethanol (10mL). The solid was

crystallized from ethanol to give 1.858g (89%) of ethyl 3-[(hydrazinothioxomethyl) amino]benzoate as white solid.

^{1}H NMR (300 MHz, d_6-DMSO): δ 9.25 (1H, s), 8.29 (1H, s), 7.88 (1H, d), 7.68 (1H, d), 7.43 (1 H, t), 4.96 (3H, br s), 4.31 (2 H, q), 1.32 (3 H, t).

Example 32: 3-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]benzoate

A solution of {3-[3-(trifluoromethyl)phenoxy]phenyl}formaldehyde (0.556g, 2.1mmol) and ethyl 3-[(hydrazinothioxomethyl)amino]benzoate (0.500g, 2.1mmol) in dry ethanol (5mL) under nitrogen refluxed 2 hours. After cooling to room temperature, the mixture was filtered and the solid washed by ethanol. The solid was suspension in dry ethanol (3.5mL) and iron (III) chloride hexahydrate (1.690g, 6.3mmol) was added. The reaction mixture was refluxed for 4 hours, then cooling to room temperature. The solid was collected by filter and washed by ethanol, then crystallized from ethyl acetate / hexanes give 0.556g (55%) of ethyl 3-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]benzoate as yellow color solid. MS $(M+H)^+$: 486; $(M-H)^-$: 484.

Example 33: Ethyl 3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy] phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl] benzoate and ethyl 3-[(2-phenylethyl) (5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazol-2-yl))amino] benzoate

To a solution of ethyl 3-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]benzoate (0.300g, 0.62mmol) in 5mL of dry DMF was added potassium carbonate (0.171g, 1.20mmol) at room temperature under an nitrogen atmosphere. After 5 minute, (2-iodoethyl)benzene (0.27mL, 1.86mmol) was injected, and the solution was stirred at 50°C for overnight. The DMF was evaporated (rotavap) under vacuum. The crude residue was purified by flash chromatography (ethyl acetate / hexanes, 100% hexanes to 1:2) to the isolation of the ethyl 3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]benzoate (0.077g) in 21% yield, R_f = 0.52 (ethyl acetate / hexanes, 1:2); MS $(M+H)^+$: 590 and the ethyl 3-[(2-phenylethyl)(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazol-2-

yl))amino]benzoate (0.037g) in 10% yield, R_f = 0.38 (ethyl acetate / hexanes, 1:2); MS $(M+H)^+$: 590.

Example 34: Compound 11: 3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl) phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]benzoic acid

To a solution of ethyl 3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy] phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]benzoate (0.075g, 0.13mmol) in 4mL of THF was added 10mL of 0.25M LiOH solution (in MeOH/H_2O, 75/25). The mixture was stirred overnight at room temperature and concentrated in vacuo. The residue added water, then added 1*N* HCl aq. solution until pH < 7. The solid was collected by filter and washed by water, then dried under vacuum give 0.068g (95%) of 3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]benzoic acid as white solid. mp. 58-59°C; MS $(M+H)^+$ 562; $(M-H)^-$ 560.

Example 35: Compound 12: 3-[(2-phenylethyl)(5-{3-[3-(trifluoromethyl) phenoxy]phenyl}(1,3,4-thiadiazol-2-yl))amino]benzoic acid

To a solution of ethyl 3-[(2-phenylethyl)(5-{3-[3-(trifluoromethyl)phenoxy]phenyl} (1,3,4-thiadiazol-2-yl))amino]benzoate (0.035g, 0.06mmol) in 4mL of THF was added 10mL of 0.25M LiOH solution (in MeOH/H_2O, 75/25). The mixture was stirred overnight at room temperature and concentrated in vacuo. The residue added water, then added 1N HCl aq. solution until pH < 7. The solid was collected by filter and washed by water, then dried under vacuum give 0.030g (90%) of 3-[(2-phenylethyl)(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazol-2-yl))amino]benzoic acid as light yellow solid. mp. 92-93°C; MS $(M+H)^+$ 562; $(M-H)^-$ 560.

Example 36: Compound 13: 1-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl) phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]benzene-3-carbohydroxamic acid

To a solution of Compound 11 (0.054g, 0.096mmol, see Example 33) and 2H-3,4,5,6-tetrahydropyran-2-yloxyamine (0.012g, 0.106mmol) in 5mL of methylene chloride was added HOBt (0.013g, 0.096mmol), followed by DMAP (0.023g, 0.19mmol), then EDC

(0.037g, 0.19mmol) at 0°C. The reaction mixture was stirred at room temperature under nitrogen for overnight. The methylene chloride was evaporated (rotavap) under vacuum. The crude residue was purified by flash chromatography (ethyl acetate / hexanes, 100% hexanes to 1:2) to give 0.054g (85%) of N-(2H-3,4,5,6-tetrahydropyran-2-yloxy){3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]phenyl}carboxamide as colorless oil. MS $(M+H)^+$ 661.

A mixture of N-(2H-3,4,5,6-tetrahydropyran-2-yloxy){3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]phenyl} carboxamide (0.054g, 0.08mmol) and PTSA (0.030g) in dry methanol (20mL) was stirred at room temperature for overnight. Then added 0.25M LiOH solution until pH > 7. The methanol was evaporated, and the residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give 0.042g (90%) of 1-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy] phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]benzene-3-carbohydroxamic acid as yellow solid. MS $(M+H)^+$ 577; $(M-H)^-$ 575.

Example 37: 1-{3-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]phenyl}ethan-1-one

To a solution of {3-[3-(trifluoromethyl)phenoxy]phenyl}formaldehyde (8.29mL, 40mmol) in acetone (75mL) at 0°C was drop wise added Jones reagent (prepared from 5.34g of CrO_3, 4.6mL of conc. H_2SO_4 and 4.4mL of H_2O) until the orange color persisted. The reaction mixture was slowly warmed up to room temperature and stirred for overnight. The isopropanol (0.5mL) was added to the reaction mixture and stirred for 2 hours. The reaction mixture was passed through Celite and concentrated (rotavap) under vacuum. The crude residue was purified by flash chromatography (ethyl acetate / hexanes / acetic acid, 100% hexanes to 1:2:0.01) to isolate the 3-[3-(trifluoromethyl) phenoxy]benzoic acid (4.80g) in 43% yield as white solid.

To a solution of 3-[3-(trifluoromethyl)phenoxy]benzoic acid (5.64g, 20mmol) and MeOH (0.81mL, 20mmol) in acetonitrile (50mL) was drop wise added (trimethylsilyl) diazomethane (2M solution in hexane, 15.00mL, 30mmol) at room temperature. After stirring overnight, the acetic acid was added to the reaction mixture to quench the excess (trimethylsilyl)diazomethane. The reaction mixture was evaporated (rotavap) under vacuum. The crude residue was purified by flash chromatography (ethyl acetate / hexanes, 100% hexanes to 1:9) to give the methyl 3-[3-(trifluoromethyl)phenoxy] benzoate (5.40g) in 92% yield as colorless oil.

^{1}H NMR: (300 MHz, d_1-$CDCl_3$) δ 7.85 (1H, d), 7.69 (1H, s), 7.49-7.43 (2H, m), 7.38 (1H, d), 7.30-7.23 (2H, m), 7.17 (1H, d), 3.91 (3H, s).

A mixture of methyl 3-[3-(trifluoromethyl)phenoxy]benzoate (1.00g, 3.38mmol) and hydrazine monohydrate (0.338g; 6.78mmol) was heated in ethanol (5mL) at reflux for overnight. The ethanol was evaporated (rotavap) under vacuum. The crude residue was washed with water and hexanes, then dried under vacuum to give 1-[3-(trifluoromethyl) phenoxy]benzene-3-carbohydrazide as white solid (0.950g, 95%).

^{1}H NMR: (300 MHz, DMSO-d_6) δ9.87 (1H, s), 7.68-7.60 (2H,m), 7.54-7.49 (3H, m), 7.36-7.31 (2H, m), 7.25 (1H, dd), 4.46 (2H, br s).

To a solution of 1-(3-Isothiocyanato-phenyl)-ethanone (0.180g; 1mmol) in toluene (10mL) is added 1-[3-(trifluoromethyl)phenoxy]benzene-3-carbohydrazide (0.300g; 1mmol) under argon. The reaction mixture is heated at reflux for two hours. The mixture is filtered while the toluene still is warm. The solid is washed with hexanes and dried to yield N-({[(3-acetylphenyl)amino]thioxomethyl}amino){3-[3-(trifluoromethyl) phenoxy]phenyl}carboxamide. The product is used for the next step without further purification.

To a slurry mixture of the above carbothioamide in toluene (5mL) at 0°C is dropped conc. H_2SO_4 (0.4mL). The reaction mixture is stirred at room temperature for three hours. The ice-H_2O (50mL) was added to the reaction mixture. The mixture is neutralized with $NH_3 \cdot H_2O$ until pH 8 and filtered. The solid product is recrystallized with MeOH/EA to yield 1-{3-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]phenyl} ethan-1-one (0.158g, 35%) as yellow solid. MP: 130-133°C.

^{1}H NMR (300 MHz, d_1-$CDCl_3$): δ 9.67 (1 H, s), 8.09 (1 H, s), 7.75-7.20 (10 H, m), 7.10 (1 H, d), 2.65 (3 H, s).

Example 38: 1-{3-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]phenyl}ethan-1-one and 1-{3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]phenyl}ethan-1-one

To a solution of 1-{3-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]phenyl}ethan-1-one (0.200g, 0.44mmol) in 4mL of dry DMF was added potassium carbonate (0.121g, 0.88mmol) at room temperature under a nitrogen atmosphere. After 5 minute, (2-iodoethyl)benzene (0.19mL, 1.30mmol) was injected, and the solution was stirred at 50°C for overnight. The DMF was evaporated (rotavap) under vacuum. The crude residue was purified by flash chromatography (ethyl acetate / hexanes, 100% hexanes to 1:2) to the isolation of the 1-{3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]phenyl}ethan-1-one (0.066g) in 27% yield, R_f = 0.55 (ethyl acetate / hexanes, 1:2); MS $(M+H)^+$: 560 and the 1-{3-[(2-phenylethyl)(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazol-2-yl))amino]phenyl}ethan-1-one (0.044g) in 18% yield, R_f = 0.35 (ethyl acetate / hexanes, 1:2); MS $(M+H)^+$: 560.

Example 39: Compound14: 2-((1E)-1-aza-2-{3-[(2-phenylethyl)(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazol-2-yl))amino]phenyl}prop-1-enyloxy)acetic acid

To a solution of 1-{3-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]phenyl}ethan-1-one (0.200g, 0.44mmol) in 4mL of dry DMF was added potassium carbonate (0.121g, 0.88mmol) at room temperature under a nitrogen atmosphere. After 5 minute, (2-iodoethyl)benzene (0.19mL, 1.30mmol) was injected, and the solution was stirred at 50°C for overnight. The DMF was evaporated (rotavap) under vacuum. The crude residue was purified by flash chromatography (ethyl acetate / hexanes, 100% hexanes to 1:2) to the isolation of the 1-{3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]phenyl}ethan-1-one (0.066g) in 27% yield, $R_f = 0.55$ (ethyl acetate / hexanes, 1:2); MS $(M+H)^+$: 560 and the 1-{3-[(2-phenylethyl)(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazol-2-yl))amino]phenyl}ethan-1-one (0.044g) in 18% yield, $R_f = 0.35$ (ethyl acetate / hexanes, 1:2); MS $(M+H)^+$: 560.

Example 40: Compound 15: 2-((1E)-1-aza-2-{3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl] phenyl}prop-1-enyloxy)acetic acid

To a solution of 1-{3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]phenyl}ethan-1-one (0.066g, 0.12mmol) and carboxymethoxylamine hemihydrochloride (0.031g, 0.14mmol) in 5mL of ethanol was added triethylamine (0.016mL, 0.14mmol) at room temperature. The mixture was refluxed for overnight and concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), concentrated, and purified by flash chromatography (ethyl acetate / hexanes/ acetic acid, 1:2:0 to 1:2:0.01) to the isolation of the 2-((1E)-1-aza-2-{3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]phenyl}prop-1-enyloxy)acetic acid (0.063g) in 85% yield;
MS $(M+H)^+$ 633; $(M-H)^-$ 631.

The reaction described in above was repeated, but using 0.044g (0.08mmol) of 1-{3-[(2-phenylethyl)(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazol-2-yl))amino]phenyl}ethan-1-one, 0.021g (0.094mmol) of carboxymethoxylamine

hemihydrochloride, and 0.013mL (0.094mmol) of triethylamine to yield 0.034g (68%) of 2-((1E)-1-aza-2-{3-[(2-phenylethyl)(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazol-2-yl))amino]phenyl}prop-1-enyloxy)acetic acid; MS $(M+H)^+$ 633.

Example 41: Methyl(2-morpholin-4-ylethyl)amine

A mixture of formic acid (67mL) and Acetic anhydride (24mL) was added drop wise to a solution 2-morpholin-4-ylethyl amine (6.5g, 50mmol) in formic acid (85% 60mL). The mixture was stirred at room temperature for overnight and then at 50°C for 2 hours. The solvents were rotovaped under reduced pressure and dried under high vacuum. This residue (N-(2-Morpholin-4-yl-ethyl)-formamide) contained 2 molecules of formic acid. This was used without purification in the next reaction. Yield: 6.3g (80%).

^{1}H NMR: (300 MHz, $CDCL_3$): 8.18 δ (1H s); 3.93 δ (4H m); 3.72 δ (2H q); 3.15 δ (6H m). MS, Observed $(M+2H)^+ = 160$.

The N-(2-Morpholin-4-yl-ethyl)-formamide (6.25g, 25mmol) was added slowly over a period of 1 hour to a cold and dry suspension of Lithium aluminum hydride (2.85g) in dry THF (100mL). The mixture was stirred in cold for 2 hours and then overnight at room temperature. Small amount of water is added to decompose aluminum salt, the solid formed was filtered off, the solid was washed with THF. The washings and filtrate were combined and the solvent removed *in vacuo* to yield the title compound.
Yield: 2.0g (55%).

Example 42: Compound 16: N1-{Biphenyl-4-yl-[methyl-(2-morpholin-4-yl-ethyl)-carbamoyl]-methyl}-N4-hydroxy-2-isobutyl-succinamide:

N1-{Biphenyl-4-yl-[methyl-(2-morpholin-4-yl-ethyl)-carbamoyl]-methyl}-N4-hydroxy-2-isobutyl-succinamide was prepared using the procedure as in Example 7 with 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}-2-(4-phenylphenyl)acetic acid (1.985g, 5mmol), methyl(2-morpholin-4-ylethyl)amine (0.87g, 6mmol), EDC HCl (1.92g, 10mmol), anhydrous hdyroxbenzotriazole (0.68g, 5mmol), N-methylmorpholine

(1.1mL, 10mmol), and methelenechloride (20mL). After workup a methyl (3R)-5-methyl-3-(N-{[N-methyl-N-(2-morpholin-4-ylethyl)carbamoyl](4-phenylphenyl)methyl}carbamoyl)hexanoate was obtained as a white solid. Yield: 225mg (10%). This intermediate (220mg, 042mmoles) was converted to the title compound using the procedure in Example 2. Yield: 33mg (15%). MS: ($M+H^+$): 525.

Compound 42: 2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-({N-[(4-methylphenyl)methyl] carbamoyl(4-phenylphenyl)methyl)pentanamide

Methyl (3R)-5-methyl-3-[N-({N-[(4-methylphenyl)methyl]carbamoyl}(4-phenyl phenyl) methyl) carbamoyl]hexanoate was prepared from 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}-2-(4-phenylphenyl)acetic acid (298mg, 0.75mmol), 4-methylbenzylamine (95μL, 0.75mmol), EDC HCl (288mg, 1.5mmol), HOBt (101mg, 0.75mmol), DIEA (261μL, 1.5mmol) and dichloromethane (10mL) using the procedure from Example 3. Yield: 280mg (56%).

2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-({N-[(4-methylphenyl)methyl] carbamoyl(4-phenylphenyl)methyl)pentanamide (47/53) was prepared from methyl (3R)-5-methyl-3-[N-({N-[(4-methylphenyl)methyl]carbamoyl}(4-phenyl phenyl) methyl) carbamoyl]hexanoate (250mg, 0.5mmol) using the procedure from Example 2. Yield: 220mg (87%). MS ($M+H^+$) 502.

Example 43: Compound 17: 2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-{(5-phenyl(2-thienyl))[N-benzylcarbamoyl]methyl}pentanamide

Prepared in a manner similar to that described in Example 28 using 0.188g (1.0mmol) of 5-phenylthiophene-2-carbaldehyde, 0.188g (1mmol) of (2R)-2-[(methoxycarbonyl) methyl]-4-methylpentanoic acid, 0.122mL (1mmol) of benzyl isocyanide and 1mL (2mmol) of 2M solution of ammonia in methanol to yield 0.088g (18%) of methyl (3R)-5-methyl-3-(N-{(5-phenyl(2-thienyl))[N-benzylcarbamoyl]methyl}carbamoyl)hexanoate. MS $(M+H)^+$ 493; $(M+HCO_2^-)^-$ 537.

Prepared in a manner similar to that described in Example 29 using 0.088g (0.18mmol) of methyl (3R)-5-methyl-3-(N-{(5-phenyl(2-thienyl))[N-benzylcarbamoyl]methyl}carbamoyl)hexanoate to yield 0.080g (90%) of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R,S)(5-phenyl(2-thienyl))[N-benzylcarbamoyl]methyl}-4-methylpentanamide (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 494; $(M-H)^-$ 492.

Example 44: Compound 18: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(9-ethylcarbazol-3-yl)[N-benzylcarbamoyl]methyl}-4-methylpentanamide

Prepared in a manner similar to that described in Example 28 using 0.223g (1.0mmol) of 9-ethylcarbazole-3-carbaldehyde, 0.188g (1mmol) of (2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoic acid, 0.122mL (1mmol) of benzyl isocyanide and 1mL (2mmol) of 2M solution of ammonia in methanol to yield 0.124g (23%) of methyl (3R)-3-(N-{(9-ethylcarbazol-3-yl)[N-benzylcarbamoyl]methyl}carbamoyl)-5-methylhexanoate. MS $(M+H)^+$ 528; $(M+HCO_2^-)^-$ 572.

Prepared in a manner similar to that described in Example 29 using 0.124g (0.23mmol) of methyl (3R)-3-(N-{(9-ethylcarbazol-3-yl)[N-benzylcarbamoyl]methyl}carbamoyl)-5-methylhexanoate to yield 0.088g (71%) of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S,R)(9-ethylcarbazol-3-yl)[N-benzylcarbamoyl]methyl}-4-methylpentanamide (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 529; $(M-H)^-$ 527.

Example 45: Compound 19: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(N-indan-2-ylcarbamoyl)[4-(3-methoxyphenyl)phenyl]methyl}-4-methylpentanamide

To solution of (2S)-2-[(tert-butoxy)carbonylamino]-2-(4-hydroxyphenyl)acetic acid (8.80g, 32.9mmol) in 40mL of MeOH was added cesium carbonate (5.364g, 16.5mmol) at room temperature under an nitrogen atmosphere. When evolution of carbon dioxide ceased, the MeOH was evaporated under vacuum. The residue was dissolved in 40mL of DMF and stirred with benzyl bromide (5.9mL, 49.4mmol) at room temperature for overnight. The NMF was evaporated under vacuum. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and purified by flash chromatography (ethyl acetate / hexanes,

100% hexanes to 1:2) to give the white solid of the phenylmethyl (2S)-2-[(tert-butoxy)carbonylamino]-2-(4-hydroxyphenyl)acetate (8.45g) in 72% yield.
MS $(M-H)^-$ 356.

To a mixture of phenylmethyl (2S)-2-[(tert-butoxy)carbonylamino]-2-(4-hydroxyphenyl) acetate (8.45g, 23.6mmol) in 22mL of CH_2Cl_2 which contained pyridine (4.78mL, 59.1mmol) at –15°C was added trifluoromethanesulfonic anhydride (4.77mL, 28.4mmol). The mixture was stirred for 5 min, the reaction quenched with water and the mixture washed with 0.5N NaOH (2 x 30mL), 15% citric acid (2 x 30mL) and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to yield 10.60g (92%) of phenylmethyl (2S)-2-[(tert-butoxy)carbonylamino]-2-{4-[(trifluoromethyl)sulfonyloxy] phenyl}acetate as light yellow solid.

^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (2H, d), 7.32-7.16 (7H, m)5.67 (1H, d), 5.40 (1H, d), 5.16 (2H, s), 1.43 (9H, s).

Tetrakis(triphenylphosphine)palladium(0) (0.071g, 0.061mmol) was added to a suspension of 3-methoxyphenylboronic acid (0.621g, 4.1mmol) and potassium carbonate (0.424g, 3.1mmol) in 12mL of toluene. The reaction mixture was degassed and heated to 80°C before adding the phenylmethyl (2S)-2-[(tert-butoxy)carbonylamino]-2-{4-[(trifluoromethyl)sulfonyloxy]phenyl}acetate (1.00g, 2.0mmol). The thick suspension was stirred at 80°C for 2 hours and then filtered through Celite. The filtrate was concentrated and purified by flash chromatography (ethyl acetate / hexanes, 100% hexanes to 1:4) to give the white solid of the phenylmethyl (2S)-2-[(tert-butoxy)carbonylamino]-2-[4-(3-methoxyphenyl)phenyl]acetate (0.878g) in 98% yield.
MS $(M-H)^-$ 446.

Prepared in a manner similar to that described in Example 4 using 0.878g (1.96mmol) of phenylmethyl (2S)-2-[(tert-butoxy)carbonylamino]-2-[4-(3-methoxyphenyl)phenyl]

acetate, and 10mL of 4M solution of HCl in 1,4-dioxane to yield 0.740g (98%) of phenylmethyl (2S)-2-amino-2-[4-(3-methoxyphenyl)phenyl]acetate, hydrochloride. MS $(M-Cl)^+$ 348.

Prepared in a manner similar to that described in Example 24 using 0.540g (1.41mmol) of phenylmethyl (2S)-2-amino-2-[4-(3-methoxyphenyl)phenyl]acetate, hydrochloride, 0.265g (1.41mmol) of (2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoic acid, 0.215g (1.41mmol) of HOBt, 0.539g (2.81mmol) of EDC, and 0.46mL (4.22mmol) of NMM to yield 0.692g (95%) of methyl (3R)-3-(N-{(1S)[4-(3-methoxyphenyl)phenyl] [benzyloxycarbonyl]methyl}carbamoyl)-5-methylhexanoate. MS $(M+H)^+$ 518; $(M+HCO_2^-)^-$ 562.

Prepared in a manner similar to that described in Example 21 using 0.692g (1.34mmol) of methyl (3R)-3-(N-{(1S)[4-(3-methoxyphenyl)phenyl][benzyloxycarbonyl]methyl} carbamoyl)-5-methylhexanoate, 0.151g 10% palladium on carbon, and 30mL of ethyl acetate to yield 0.567g (99%) of 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}(2S)-2-[4-(3-methoxyphenyl)phenyl]acetic acid. MS $(M+H)^+$ 428; $(M-H)^-$ 426.

Prepared in a manner similar to that described in Example 24 using 0.467g (1.09mmol) of 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}(2S)-2-[4-(3-methoxyphenyl)phenyl]acetic acid, 0.145g (1.09mmol) of indane-2-ylamine, 0.167g (1.09mmol) of HOBt, 0.419g (2.18mmol) of EDC, and 0.24mL (2.18mmol) of NMM to yield 0.501g (85%) of methyl (3R)-3-(N-{(N-indan-2-ylcarbamoyl)[4-(3-methoxyphenyl) phenyl]methyl}carbamoyl)-5-methylhexanoate. MS $(M+H)^+$ 543.

Prepared in a manner similar to that described in Example 29 using 0.501g (0.92mmol) of methyl (3R)-3-(N-{(N-indan-2-ylcarbamoyl)[4-(3-methoxyphenyl)phenyl]methyl} carbamoyl)-5-methylhexanoate to yield 0.414g (82%) of 2-(N-hydroxycarbamoylmethyl)

(2R)-N-{(1S,R)(N-indan-2-ylcarbamoyl)[4-(3-methoxyphenyl)phenyl]methyl}-4-methylpentanamide (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 544.

Example 46: Compound 20:
2-(N-hydroxycarbamoylmethyl)(2R)-N-((1R){N-[2-(dimethylamino)ethyl]-N-benzylcarbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide

Following the procedure of Example 3, N'-benzyl-N,N-dimethylethylenediamine (673mg, 3.77mmol), 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}-2-(4-phenylphenyl)acetic acid (1.5g, 3.7mmol), EDC (1.44g, 7.54mmol), HOBt (577mg, 3.77mmol), NMM instead of DIEA (0.828mL, 7.54mmol) and dichloromethane (50mL) to yield 1.24g(59%) of methyl (3R)-3-[N-({N-[2-(dimethylamino)ethyl]-N-benzylcarbamoyl}(4-phenylphenyl)methyl)carbamoyl]-5-methylhexanoate as a yellow liquid. MS $(M+H)^+$558.

Using the procedure of Example 2, methyl (3R)-3-[N-({N-[2-(dimethylamino)ethyl]-N-benzylcarbamoyl}(4-phenylphenyl)methyl)carbamoyl]-5-methylhexanoate (257mg, 0.46mmol). The crude product was purified by silica gel chromatography (water/methanol, 30:70) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-((1R){N-[2-(dimethylamino)ethyl]-N-benzylcarbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide (45mg) in 18% yield (less polar product), $R_f = 0.41$ (methanol). MS $(M+H)^+$544.

Example 47: Compound 21:
2-(N-hydroxycarbamoylmethyl)(2R)-N-({N-[(2,6-dimethoxyphenyl)methyl] carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide

Following the procedure of Example 3, 2,6-dimethoxybenzylamine (84mg, 0.5mmol), 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}-2-(4-phenylphenyl)acetic acid (200mg, 0.5mmol), EDC (192mg, 1mmol), HOBt (77mg, 0.5mmol), NMM instead of DIEA (0.11mL, 1mmol) and dichloromethane (20mL) to yield 257mg(94%) of methyl (3R)-3-[N-({N-[(2,6-dimethoxyphenyl)methyl]carbamoyl}(4-phenylphenyl)methyl) carbamoyl]-5-methylhexanoate as an off white solid. MS $(M+H)^+$547.

Using the procedure of Example 2, methyl (3R)-3-[N-({N-[(2,6-dimethoxyphenyl) methyl]carbamoyl}(4-phenylphenyl)methyl)carbamoyl]-5-methylhexanoate (240mg, 0.44mmol). The crude product was purified by heating in dichloromethane to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-({N-[(2,6-dimethoxyphenyl)methyl] carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide (180mg) in 75% yield (diastereoisomeric mixture of 37/54.5 ratio), $R_f = 0.47$ (ethyl acetate/methanol, 9:1). MS $(M+H)^+548$.

Example 48: Compound 22:
2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)[N-methyl-N-(2-pyridylmethyl)carbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide

Following the procedure of Example 3, methylpyridin-2-ylmethylamine dihydrochloride (49mg, 0.25mmol), 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}-2-(4-phenylphenyl)acetic acid (100mg, 0.25mmol), EDC (96mg, 0.5mmol), HOBt (38mg, 025mmol), NMM instead of DIEA (0.109mL, 1mmol) and dichloromethane (10mL) to yield 100mg(80%) of methyl (3R)-5-methyl-3-(N-{[N-methyl-N-(2-pyridylmethyl) carbamoyl](4-phenylphenyl)methyl}carbamoyl)hexanoate as a yellow liquid. MS $(M+H)^+502$.

Using the procedure of Example 2, methyl (3R)-5-methyl-3-(N-{[N-methyl-N-(2-pyridylmethyl)carbamoyl](4-phenylphenyl)methyl}carbamoyl)hexanoate (99mg, 0.197mmol). The crude product was purified by silica gel chromatography (water/methanol, 40:60) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)[N-methyl-N-(2-pyridylmethyl)carbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide (10mg) in 10% yield (diastereoisomeric mixture of 89/11 ratio), $R_f = 0.52$ (ethyl acetate/methanol, 4:1). MS $(M+H)^+503$.

Example 49: Compound 23:
2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)[N-methyl-N-(2-pyridylmethyl) carbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide

Using the procedure of Example 2, methyl (3R)-5-methyl-3-(N-{[N-methyl-N-(2-pyridylmethyl)carbamoyl](4-phenylphenyl)methyl}carbamoyl)hexanoate (99mg, 0.197mmol). The crude product was purified by silica gel chromatography (water/methanol, 30:70) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)[N-methyl-N-(2-pyridylmethyl)carbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide (15mg) in 15% yield (less polar product), $R_f = 0.35$ (ethyl acetate/methanol, 4:1). MS $(M+H)^+$503.

Example 50: Compound 24: 2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-{[N-methyl-N-(2-(2-pyridyl)ethyl)carbamoyl](4-phenylphenyl)methyl}pentanamide

Following the procedure of Example 3, 2-(2-methylaminoethyl)pyridine (34mg, 0.25mmol), 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}-2-(4-phenylphenyl)acetic acid (100mg, 0.25mmol), EDC (96mg, 0.5mmol), HOBt (38mg, 025mmol), NMM instead of DIEA (0.055mL, 0.5mmol) and dichloromethane (10mL) to yield 115mg (89%) of methyl (3R)-5-methyl-3-(N-{[N-methyl-N-(2-(2-pyridyl)ethyl) carbamoyl](4-phenylphenyl)methyl}carbamoyl)hexanoate as a yellow liquid. MS $(M+H)^+$516.

Using the procedure of Example 2, methyl (3R)-5-methyl-3-(N-{[N-methyl-N-(2-(2-pyridyl)ethyl)carbamoyl](4-phenylphenyl)methyl}carbamoyl)hexanoate (113mg, 0.22mmol). The crude product was purified by silica gel chromatography (water/methanol, 30:70) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-{[N-methyl-N-(2-(2-pyridyl)ethyl)carbamoyl](4-phenylphenyl)methyl} pentanamide (13mg) in 11% yield (diastereoisomeric mixture of 45/55 ratio), $R_f = 0.48$ (ethyl acetate/methanol, 4:1). MS $(M+H)^+$517.

Example 51: Compound 25: 2-[2-(N-hydroxycarbamoylmethyl)(2R)-4-methylpentanoylamino](2S)-N-indan-2-yl-N'-indan-2-ylpentane-1,5-diamide

Following the procedure of Example 3, boc-glu(obzl)-OH (1g, 2.9mmol), 2-aminoindan (395mg, 2.9mmol), EDC (1.11g, 5.8mmol), HOBt (444mg, 2.9mmol), NMM instead of

DIEA (0.637mL, 5.8mmol) and dichloromethane (15mL) to yield 900mg (69%) of phenylmethyl (4S)-4-[(tert-butoxy)carbonylamino]-4-(N-indan-2-ylcarbamoyl)butanoate as a brown solid.

^{1}H NMR (300MHz,d_6-DMSO): δ 8.121 (1H,d), 7.19 (9H,m), 6.86 (1H,d), 5.07 (2H,s), 4.44 (1H, q), 3.9 (1H, q), 3.16 (2H, q), 2.76 (2H, m), 2.35 (2H, t), 1.78 (2H, m), 1.35 (9H, s).

Using the procedure of Example 21, phenylmethyl (4S)-4-[(tert-butoxy)carbonylamino]-4-(N-indan-2-ylcarbamoyl)butanoate (890mg, 1.96mmol) 10% palladium on carbon (89mg, 10% of ester), methanol (20mL) to yield 700mg (98%) of (4S)-4-[(tert-butoxy) carbonylamino]-4-(N-indan-2-ylcarbamoyl)butanoic acid as a white solid. $(M-H)^-$ 361.

Following the procedure of Example 3, (4S)-4-[(tert-butoxy)carbonylamino]-4-(N-indan-2-ylcarbamoyl)butanoic acid (690mg, 1.9mmol), 2-aminoindan (252mg, 1.9mmol), EDC (730mg, 3.8mmol), HOBt (291mg, 1.9mmol), NMM instead of DIEA (0.417mL, 3.8mmol) and dichloromethane (15mL) to yield 887mg (98%) of (2S)-2-[(tert-butoxy) carbonylamino]-N-indan-2-yl-N'-indan-2-ylpentane-1,5-diamide as a off white solid. .

^{1}H NMR (300MHz,d_6-DMSO): δ 8.10 (2H,t), 7.15 (8H, m), 6.74 (2H, m), 3.84 (1H, m), 3.17 (3H,m), 2.74 (4H, m), 2.06 (2H, q), 1.71 (2H,m), 1.35 (9H, s).

Following the procedure of Example 4, (2S)-2-[(tert-butoxy)carbonylamino]-N-indan-2-yl-N'-indan-2-ylpentane-1,5-diamide (870mg, 1.8mmol) and 4N HCl/Dioxane (10mL) to yield 714mg (96%) of (2S)-2-amino-N-indan-2-yl-N'-indan-2-ylpentane-1,5-diamide hydrochloride as a brown solid. $(M+H-HCl)^+$ 378.

Following the procedure of Example 3, (2S)-2-amino-N-indan-2-yl-N'-indan-2-ylpentane-1,5-diamide hydrochloride (300mg, 0.7mmol), (2R)-2-[(methoxycarbonyl) methyl]-4-methylpentanoic acid (136mg, 0.7mmol), EDC (269mg, 1.4mmol), HOBt

(107mg, 0.7mmol), NMM instead of DIEA (0.23mL, 2.1mmol) and dichloromethane (10mL) to yield 352mg (92%) of methyl (3R)-3-{N-[(1S)-1,3-bis(N-indan-2-ylcarbamoyl)propyl]carbamoyl}-5-methylhexanoate as a off white solid. MS $(M+H)^+$.

^1H NMR (300MHz,d_6-DMSO): δ 8.04 (2H, d), 7.17 (8H,d), 4.43 (2H,m), 4.15 (1H,m), 3.49 (3H,m), 3.14 (4H,m), 2.71 (5H,m), 2.42 (2H,m), 2.061(2H,m), 1.76 (2H, m), 1.41 (2H, m), 1.1 (1H, m), 0.81 (6H, m)

Using the procedure of Example 2, methyl (3R)-3-{N-[(1S)-1,3-bis(N-indan-2-ylcarbamoyl)propyl]carbamoyl}-5-methylhexanoate (340mg, 0.62mmol) was converted to 2-[2-(N-hydroxycarbamoylmethyl)(2R)-4-methylpentanoylamino](2S)-N-indan-2-yl-N'-indan-2-ylpentane-1,5-diamide (320mg) in 94% yield, $R_f = 0.63$ (ethyl acetate/methanol, 4:1). MS $(M-H)^-$547.

Example 52: Compound 26: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)(4-phenylphenyl)[N-(2-pyridylmethyl)carbamoyl]methyl}-4-methylpentanamide

Following the procedure of Example 3, 2-(aminomethyl)pyridine (54mg, 0.5mmol), 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}-2-(4-phenylphenyl)acetic acid (200mg, 0.5mmol), EDC (192mg, 1mmol), HOBt (77mg, 0.5mmol), NMM instead of DIEA (0.11mL, 1mmol) and dichloromethane (10mL) to yield 214mg (88%) of methyl (3R)-5-methyl-3-(N-{(4-phenylphenyl)[N-(2-pyridylmethyl)carbamoyl]methyl} carbamoyl)hexanoate as a yellow solid. MS $(M+H)^+$488.

Using the procedure of Example 2, methyl (3R)-5-methyl-3-(N-{(4-phenylphenyl)[N-(2-pyridylmethyl)carbamoyl]methyl}carbamoyl)hexanoate (174mg, 0.35mmol). The crude product was purified by silica gel chromatography (water/methanol, 30:70) then purify by prep tlc to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)(4-phenylphenyl)[N-(2-pyridylmethyl)carbamoyl]methyl}-4-methylpentanamide (13mg) in 8% yield (less polar product), $R_f = 0.58$ (ethyl acetate/methanol, 4:1). MS $(M-H)^-$487.

Example 53: Compound 27: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)(4-phenylphenyl)[N-(2-pyridylmethyl)carbamoyl]methyl}-4-methylpentanamide

Using the procedure of Example 2, methyl (3R)-5-methyl-3-(N-{(4-phenylphenyl)[N-(2-pyridylmethyl)carbamoyl]methyl}carbamoyl)hexanoate (174mg, 0.35mmol). The crude product was purified by silica gel chromatography (water/methanol, 30:70) then purify by prep tlc to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)(4-phenylphenyl)[N-(2-pyridylmethyl)carbamoyl]methyl}-4-methylpentanamide (15mg) in 9% yield (more polar product), $R_f = 0.5$ (ethyl acetate/methanol, 4:1). MS $(M+H)^+$489.

Example 54: Compound 28: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)[N-methyl-N-benzylcarbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide

Following the procedure of Example 3, N-methylbenzylamine (61mg, 0.5mmol), 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}-2-(4-phenylphenyl)acetic acid (200mg, 0.5mmol), EDC (192mg, 1mmol), HOBt (70mg, 0.5mmol), NMM instead of DIEA (0.184mL, 1mmol) and dichloromethane (5mL) to give the product methyl (3R)-5-methyl-3-(N-{[benzyloxycarbonyl](4-phenylphenyl)methyl}carbamoyl)hexanoate as a yellow solid.

Using the procedure of Example 2, methyl (3R)-5-methyl-3-(N-{[benzyloxycarbonyl](4-phenylphenyl)methyl}carbamoyl)hexanoate (200mg, 0.4mmol). The crude product was purified by silica gel chromatography (ethyl acetate/methanol, 9:1) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)[N-methyl-N-benzylcarbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide (5mg) in 2% yield (less polar product), $R_f =$ 0.55 (ethyl acetate/methanol, 9:1). MS $(M+H)^+$502.

Example 55: Compound 29: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)[N-methyl-N-benzylcarbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide

Using the procedure of Example 2, methyl (3R)-5-methyl-3-(N-{[benzyloxycarbonyl](4-phenylphenyl)methyl}carbamoyl)hexanoate (200mg, 0.4mmol). The crude product was purified by silica gel chromatography (ethyl acetate) to the isolation of 2-(N-

hydroxycarbamoylmethyl)(2R)-N-{(1S)[N-methyl-N-benzylcarbamoyl](4-phenylphenyl) methyl}-4-methylpentanamide (14mg) in 4% yield (more polar product), $R_f = 0.74$ (ethyl acetate/methanol, 9:1). MS $(M+H)^+$502.

Example 56: Compound 30: 4-({2-[2-(N-hydroxycarbamoylmethyl)(2R)-4-methylpentanoylamino]-2-(4-phenylphenyl)acetylamino}methyl)benzoic acid

Using the procedure of Example 2, 4-[(2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}-2-(4-phenylphenyl)acetylamino)methyl]benzoic acid (155mg, 0.29mmol). The crude product was purified by silica gel chromatography (methanol/water, 70:30) to the isolation of 4-({2-[2-(N-hydroxycarbamoylmethyl)(2R)-4-methylpentanoylamino]-2-(4-phenylphenyl)acetylamino}methyl)benzoic acid (48mg) in 48% yield, $R_f = 0.55$ (ethyl acetate/methanol, 4:1). MS $(M+H)^+$531.9.

Example 57: Compound 31: 3-(N-hydroxycarbamoyl)(2R)-2-methyl-N-{[N-benzylcarbamoyl](4-phenylphenyl)methyl}propanamide

Using the procedure of Example 28, (R)-(+)-2-methylsuccinic acid 4-methyl ester (112mg, 0.77mmol), ammonia (0.77mL, 1.54mmol), 4-biphenylcarboxaldehyde (140mg, 0.77mmol), and benzyl isocyanide (90mg, 0.77mmol). The crude residue was purified by flash chromatography (dichloromethane/ methanol, 100:2) to yield 263mg (77%) of methyl (3R)-3-(N-{[N-benzylcarbamoyl](4-phenylphenyl)methyl}carbamoyl)butanoate as a yellow solid. MS $(M+H)^+$445.

Using the procedure of Example 2, methyl (3R)-3-(N-{[N-benzylcarbamoyl](4-phenylphenyl)methyl}carbamoyl)butanoate (250mg, 0.56mmol). The crude product was purified by silica gel chromatography (methanol/water, 70:30) to the isolation of 3-(N-hydroxycarbamoyl)(2R)-2-methyl-N-{[N-benzylcarbamoyl](4-phenylphenyl) methyl} propanamide (16mg) in 6% yield, $R_f = 0.35$ (ethyl acetate/methanol, 9:1).
MS $(M+H)^+$446.

Example 58: Compound 32:
2-(N-hydroxycarbamoylmethyl)(2R)-N-(1R,S)(1R,S) {N-[(3-methoxyphenyl)methyl] carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide

Methyl (3R)-3-[N-((1R,S) {N-[(3-methoxyphenyl)methyl]carbamoyl}(4-phenylphenyl)methyl) carbamoyl]-5-methylhexanoate was prepared following the procedure from Example 3 using 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoylamino}-2-(4-phenylphenyl) acetic acid (see Example 21) (200mg, 0.5mmol), 3-methoxybenzylamine (70mg, 0.5mmol), EDC HCl (192mg, 1mmol), HOBt (68mg, 0.5mmol), DIEA (184µl, 1mmol) in Dichloromethane (5mL). Yield: 210mg (81%). MS: ($M+H^+$) 517.

2-(N-hydroxycarbamoylmethyl)(2R)-N-((1R,S) {N-[(3-methoxyphenyl)methyl] carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide (43/57) was prepared from Methyl(3R)-3-[N-({N-[(3-methoxyphenyl)methyl]carbamoyl}(4-phenylphenyl)methyl) carbamoyl]-5-methylhexanoate (206mg, 0.4mmol) using the procedure from Example 2. A mixture of two diastereoisomers was obtained. Yield: 170mg (82%).
MS: ($M+H^+$) 518.

Example 59: Compound 33: 2-(N-hydroxycarbamoylmethyl)(2R)-N-((1R,S){N-[(4-{[(tert-butoxy)carbonylamino] methyl} phenyl)methyl]carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide

Methyl (3R)-3-[N-((1R,S){N-[(4-{[(tert-butoxy)carbonylamino]methyl}phenyl)methyl] carbamoyl}(4-phenylphenyl)methyl)carbamoyl]-5-methylhexanoate was prepared using the procedure in Example 3 with 2-{(2R)-2-[(methoxycarbonyl)methyl]-4-methyl pentanoylamino}-2-(4-phenylphenyl)acetic acid (200mg, 0.5mmol), 1-(N-boc-aminomethyl)-4-(aminomethyl)benzene (120mg, 0.5mmol), EDC HCl (192mg, 1mmol), HOBt (68mg, 0.5mmol), DIEA (174µL, 1mmmol) and dichloromethane (5mL). Yield: 260mg (85%). MS: ($M+H^+$) 616.

2-(N-hydroxycarbamoylmethyl)(2R)-N-((1R,S){N-[(4-{[(tert-butoxy)carbonylamino] methyl}phenyl)methyl]carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide (57/43) was prepared from methyl(3R)-3-[N-((1R,S){N-[(4-{[(tert-butoxy)carbonyl

amino]methyl}phenyl)methyl]carbamoyl}(4-phenylphenyl)methyl)carbamoyl]-5-methyl hexanoate (246mg, 0.4mmol) using the procedure from Example 2.
Yield: 150mg (60%). MS: ($M+H^+$) 617.

Example 60: Compound 34: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{[N-((1S)-1-phenylethyl)carbamoyl](3-phenylphenyl)methyl}-4-methylpentanamide

Using the procedure in Example 28, (2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoic acid (145mg, 0.77mmol), ammonia (0.77mL, 1.54mmol), 3-phenylbenzaldehyde (140mg, 0.77mmol), and (S)-(-)-alpha-methylbenzyl isocyanide (140mg, 0.77mmol). The crude residue was purified by flash chromatography (dichloromethane/ methanol, 100:1.5) to yield 194mg (50%) of methyl (3R)-3-(N-{[N-((1S)-1-phenylethyl)carbamoyl](3-phenylphenyl)methyl}carbamoyl)-5-methylhexanoate as a yellow solid. MS $(M+H)^+$501.

Using the procedure in Example 2, methyl (3R)-3-(N-{[N-((1S)-1-phenylethyl) carbamoyl](3-phenylphenyl)methyl}carbamoyl)-5-methylhexanoate (188mg, 0.376mmol). The crude product was purified by hot isopropanol to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{[N-((1S)-1-phenylethyl)carbamoyl](3-phenylphenyl) methyl}-4-methylpentanamide (43mg) in 23% yield, $R_f = 0.69$ (ethyl acetate/methanol, 9:1). MS $(M+H)^+$502.

Example 61: Compound 35: 2-(N-hydroxycarbamoylmethyl)(2R)-N-({N-[(3-methylphenyl)methyl]carbamoyl}(4-phenylphenyl)methyl)hexanamide

Following the procedure of Example 3, 3-methylbenzylamine (242mg, 2mmol), N-Boc-amino-biphenyl acetic acid (654mg, 2mmol), EDC (768mg, 4mmol), HOBt (306mg, 2mmol), NMM instead of DIEA (0.439mL, 4mmol) and dichloromethane (15mL) to yield 569mg (66%) of 2-[(tert-butoxy)carbonylamino]-N-[(3-methylphenyl)methyl]-2-(4-phenylphenyl)acetamide as a yellow solid.

Following the procedure of Example 4, 2-[(tert-butoxy)carbonylamino]-N-[(3-methylphenyl)methyl]-2-(4-phenylphenyl)acetamide (556mg, 1.3mmol) to yield 418mg

(88%) of 2-amino-N-[(3-methylphenyl)methyl]-2-(4-phenylphenyl)acetamide hydrochloride as a yellow solid.

Following the procedure of Example 3, 2-amino-N-[(3-methylphenyl)methyl]-2-(4-phenylphenyl)acetamide hydrochloride (400mg, 1.1mmol), (2R)-2-[(ethoxycarbonyl) methyl]hexanoic acid (221mg, 1.09mmol), EDC (419mg, 2.1mmol), HOBt (167mg, 1.09mmol), NMM instead of DIEA (0.359mL, 3.2mmol) and dichloromethane (10mL) to yield 510mg (91%) of ethyl (3R)-3-[N-({N-[(3-methylphenyl)methyl]carbamoyl}(4-phenylphenyl)methyl)carbamoyl]heptanoate as an yellow solid.

Using the procedure of Example 2, ethyl (3R)-3-[N-({N-[(3-methylphenyl)methyl] carbamoyl}(4-phenylphenyl)methyl)carbamoyl]heptanoate (250mg, 0.48mmol). The crude product was recrytalized in isopropanol and dichloromethane to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-({N-[(3-methylphenyl)methyl]carbamoyl}(4-phenylphenyl)methyl)hexanamide (147mg) in 61% yield.
R_f = 0.53 (ethyl acetate/methanol, 9:1). MS $(M+H)^+$502.

Example 62: Compound 36: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{fluoren-2-yl[N-benzylcarbamoyl]methyl}-4-methylpentanamide

Prepared in a manner similar to that described in Example 1 using 0.291g (1.5mmol) of fluorene-2-carbaldehyde, 0.282g (1.5mmol) of (2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoic acid, 0.182mL (1.5mmol) of benzyl isocyanide and 1.5mL (3.0mmol) of 2M solution of ammonia in methanol to yield 0.396g (53%) of methyl (3R)-3-(N-{fluoren-2-yl[N-benzylcarbamoyl]methyl}carbamoyl)-5-methylhexanoate.
MS $(M+H)^+$ 499; $(M+HCO_2^-)^-$ 543.

Prepared in a manner similar to that described in Example 29 using 0.078g (0.16mmol) of methyl (3R)-3-(N-{fluoren-2-yl[N-benzylcarbamoyl]methyl}carbamoyl)-5-methylhexanoate to yield 0.035g (44%) of 2-(N-hydroxycarbamoylmethyl)(2R)-N-

{(1S,R)fluoren-2-yl[N-benzylcarbamoyl]methyl}-4-methylpentanamide (3:2 mixture of diastereoisomers). MS $(M+H)^+$ 500; $(M-H)^-$ 498.

Example 63: Compound 37: 2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-methyl-N-{[N-benzylcarbamoyl](4-phenylphenyl)methyl}pentanamide

Prepared in a manner similar to that described in Example 1 using 0.273g (1.5mmol) of 4-phenylbenzaldehyde, 0.282g (1.5mmol) of (2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoic acid, 0.182mL (1.5mmol) of benzyl isocyanide and 1.5mL (3.0mmol) of 2M solution of methylamine in methanol to yield 0.565g (75%) of methyl (3R)-5-methyl-3-(N-methyl-N-{[N-benzylcarbamoyl](4-phenylphenyl)methyl}carbamoyl) hexanoate. MS $(M-H)^-$ 499.

Prepared in a manner similar to that described in Example 29 using 0.164g (0.33mmol) of methyl (3R)-5-methyl-3-(N-methyl-N-{[N-benzylcarbamoyl](4-phenylphenyl)methyl} carbamoyl)hexanoate to yield 0.121g (73%) of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S,R)[N-benzylcarbamoyl](4-phenylphenyl)methyl}-4-methyl-N-methylpentanamide (1:3 mixture of diastereoisomers). MS $(M-H)^-$ 500.

Example 64: Compound 38: 2-(N-hydroxycarbamoylmethyl)(2R)-N-((1R,S){N-[(3,4-dimethylphenyl)methyl] carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide

Methyl (3R)-3-[N-({N-[(3,4-dimethylphenyl)methyl]carbamoyl}(4-phenylphenyl) methyl)carbamoyl]-5-methylhexanoate was prepared from 2-{(2R)-2-[(methoxy carbonyl)methyl]-4-methyl pentanoylamino}-2-(4-phenylphenyl)acetic acid (397mg, 1mmol), 2,3-dimethylbenzylamine (135mg, 1mmol), EDC HCl (384mg, 2mmol), HOBt (135mg, 1mmol), DIEA (384μL, 2mmol), and dichloromethane (5mL) using the procedure of Example 3. Yield: 290mg (57%). MS: $(M+H^+)$ 515.

2-(N-hydroxycarbamoylmethyl)(2R)-N-((1R,S){N-[(3,4-dimethylphenyl) methyl] carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide (32/68) was prepared from methyl (3R)-3-[N-({N-[(3,4-dimethylphenyl)methyl]carbamoyl}(4-phenylphenyl)

methyl)carbamoyl]-5-methyl hexanoate (257mg, 0.5mmol) using the procedure from Example 2. Yield: 150mg (58%). MS: ($M+H^+$) 516.

Example 65: Compound 39: 2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1R,S)(N-indan-2-ylcarbamoyl)(4-phenylphenyl) methyl]hexanamide

Methyl (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy] carbamoylmethyl)hexanoate was prepared using the procedures from Example 3 using (r)-2-butylsuccinic acid-1-methyl ester (5.0g, 26.5mmol), [(2,4-dimethoxy phenyl) methyl][(4-methoxyphenyl)methoxy]amine (9.09g, 30mmol), EDC HCl (10.18g, 53mmol), HOBt (3.58g, 26.5mmol), DIEA (9.22mL, 53mmol), and dichloromethane (100mL). Yield: 11.0g (88%). MS: ($M+H^+$) 474.

(2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy] carbamoyl}methyl)hexanoic acid, sodium salt was prepared by from methyl (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy] carbamoylmethyl) hexanoate (10.4g, 22mmol) using the procedure from Example 13. Yield: 8.0g (75%). MS: ($M+H^+$-Na) 460.

2-[(tert-butoxy)carbonylamino]-N-indan-2-yl-2-(4-phenylphenyl)acetamide was prepared by heating the mixture of N-boc-amino-biphenyl acetic acid (654mg, 2.0mmol), 2-aminoindan (258μL, 2mmol) EDC HCl (768mg, 4mmol), HOBt (270mg, 2mmol), DIEA (696μL, 4mmol), dimethylformamide (5mL). The mixture was heated to 160°C for 600 seconds using microwaves. The DMF was rotovaped, the residue was taken in EtOAc and washed with 1N HCl (2 x 15mL), saturated sodium carbonate solution (2 x 15mL), finally by brine (2 x 15mL). The EtOAc solution was dried over anhydrous sodium sulphate and rotovaped. The residue on triturating with hexanes gave a solid. Yield: 0.79g (88%). MS: ($M+HCO_2^-$)$^-$ 487.

2-amino-N-indan-2-yl-2-(4-phenylphenyl)acetamide, hydrochloride was prepared from 2-[(tert-butoxy)carbonylamino]-N-indan-2-yl-2-(4-phenylphenyl)acetamide (665mg,

1.5mmol) using 4N HCl/dioxane (10mL), using the procedure from Example 4. Yield: 550mg (97%).

(2R)-N'-[((1R,S)2,4-dimethoxyphenyl)methyl]-2-butyl-N-[(N-indan-2-ylcarbamoyl)(4-phenyl phenyl) methyl]-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide was prepared from 2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl) methoxy] carbamoyl}methyl)hexanoic acid (481mg, 1mmol) 2-amino-N-indan-2-yl-2-(4-phenyl phenyl) acetamide, hydrochloride (379mg, 1mmol), EDC HCl (384mg, 2mmol), HOBt (135mg, 1mmol), DIEA (384μL, 2mmol) and dichloromethane (5mL). Yield 710mg (91%).

2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1R,S)(N-indan-2-ylcarbamoyl)(4-phenyl phenyl) methyl]hexanamide (59/41) was prepared from (2R)-N'-[((1R,S)2,4-dimethoxyphenyl) methyl]-2-butyl-N-[(N-indan-2-ylcarbamoyl)(4-phenyl phenyl) methyl]-N'-[(4-methoxy phenyl)methoxy]butane-1,4-diamide (220mg, 0.28mmol) using the procedure from Example 2. Yield: 100mg (45%). MS ($M+H^+$) 514.

Example 66: Compound 40: 2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-[(4-phenylphenyl)methyl]pentanamide

Prepared in a manner similar to that described in Example 24 using 1.00g (4.90mmol) of (2R)-2-[(methoxycarbonyl)methyl]-4-methylpentanoic acid, 0.906g (4.90mmol) of (4-phenylphenyl)methylamine, 0.757g (4.90mmol) of HOBt, 1.895g (9.89mmol) of EDC, and 1.09mL (9.89mmol) of NMM to yield 1.237g (71%) of methyl (3R)-5-methyl-3-{N-[(4-phenylphenyl)methyl]carbamoyl}hexanoate. MS $(M+H)^+$ 354; $(M+HCO_2^-)^-$ 398.

Prepared in a manner similar to that described in Example 29 using 2.856g (8.06mmol) of methyl (3R)-5-methyl-3-{N-[(4-phenylphenyl)methyl]carbamoyl}hexanoate to yield 1.050g (37%) of 2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-[(4-phenylphenyl) methyl]pentanamide. MS $(M+H)^+$ 355; $(M-H)^-$ 353.

Example 67: Compound 43: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-(4-(2-naphthyl)phenyl)ethyl}-4-methylpentanamide

Following the procedure of Example 3, Boc-P-bromo-Phe-OH (3.4g, 10mmol), (2S)-2-amino-4-methylpentanamide (1.3g, 10mmol), EDC (3.8g, 20mmol), HOBt (1.5g, 10mmol), NMM instead of DIEA (3.48mL, 20mmol) and dichloromethane (90mL) to yield 4.3g (94%) of (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(tert-butoxy) carbonylamino]-3-(4-bromophenyl)propanamide as an white solid.

Following the procedure of Example 4, (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(tert-butoxy)carbonylamino]-3-(4-bromophenyl)propanamide (4.3g, 9.3mmol) to yield 3.6g (98%) of (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-3-(4-bromophenyl) propanamide as a white solid.

Following the procedure of Example 22, (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-3-(4-bromophenyl)propanamide (392mg, 1mmol), 2-naphthaleneboronic acid (172mg, 1mmol), bis(triphenylphosphine) palladium dichloride (35mg, 0.05mmol), 1M sodiumcarbonate solution (3mL) and acetonitrile (2mL) to yield 307mg (76%) of N-((1R)-1-carbamoyl-3-methylbutyl)(2S)-2-amino-3-(4-(2-naphthyl)phenyl)propanamide an off white solid.

Following the procedure of Example 3, N-((1R)-1-carbamoyl-3-methylbutyl)(2S)-2-amino-3-(4-(2-naphthyl)phenyl)propanamide (275mg, 0.68mmol), (2R)-2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid (137mg, 0.68mmol), EDC (261mg, 1.36mmol), HOBt (104mg, 0.68mmol), NMM instead of DIEA (0.149mL, 1.36mmol) and dichloromethane (10mL) to yield 192mg(48%) of ethyl (3R)-3-(N-{(1R)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-(4-(2-naphthyl)phenyl)ethyl}carbamoyl)-5-methylhexanoate as an yellow solid.

Using the procedure of Example 2, ethyl (3R)-3-(N-{(1R)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-(4-(2-naphthyl)phenyl)ethyl}carbamoyl)-5-methylhexanoate (135mg, 0.23mmol). The crude product was recrytallized in ethyl acetate to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{1-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-2-(4-(2-naphthyl)phenyl)ethyl}-4-methylpentanamide (100mg) in 76% yield, $R_f = 0.68$ (ethyl acetate/methanol, 4:1). MS (M+H)$^-$573.

Example 68: Compound 44: 2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-1-(N-indan-2-ylcarbamoyl)-2-(5-phenyl(2-thienyl))ethyl]hexanamide

Following the procedure of Example 3, 2-aminoindan (665mg, 5mmol), (S)-N-Boc-2-(5-bromothienyl)-alanine (1.75g, 5mmol), EDC (1.9g, 10mmol), HOBt (765mg, 5mmol), NMM instead of DIEA (1.1mL, 10mmol) and dichloromethane (20mL) to yield 1.4g (59%) of (2R)-N-[(1S)-1-(N-indan-2-ylcarbamoyl)-2-(5-phenyl(2-thienyl))ethyl]-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide as a white solid.

Following the procedure of Example 22, (2R)-N-[(1S)-1-(N-indan-2-ylcarbamoyl)-2-(5-phenyl(2-thienyl))ethyl]-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide (698mg, 1.5mmol), phenylboronic acid (183mg , 1.5mmol), bis(triphenylphosphine) palladium dichloride (53mg, 0.075mmol), 1M sodiumcarbonate solution (3mL) and acetonitrile (2mL). The crude residue was purified by flash chromatography (hexanes/ethyl acetate, 1:1) to yield 550mg (79%) of (2S)-2-[(tert-butoxy)carbonylamino]-N-indan-2-yl-3-(5-phenyl(2-thienyl))propanamide as a white solid.

Following the procedure of Example 4, (2S)-2-[(tert-butoxy)carbonylamino]-N-indan-2-yl-3-(5-phenyl(2-thienyl))propanamide (542mg, 1.2mmol) to yield 466mg (99%) of (2S)-2-amino-N-indan-2-yl-3-(5-phenyl(2-thienyl))propanamidehydrochloride as a yellow solid.

Following the procedure of Example 3, (2S)-2-amino-N-indan-2-yl-3-(5-phenyl(2-thienyl))propanamidehydrochloride (358mg, 0.9mmol), (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy]carbamoyl}methyl)hexanoic acid, sodium salt (433mg, 0.9mmol), EDC (346mg, 1.8mmol), HOBt (138mg, 0.9mmol), NMM instead of DIEA (0.198mL, 1.8mmol) and dichloromethane (15mL) to yield 527mg (73%) of (2R)-N-[(1S)-1-(N-indan-2-ylcarbamoyl)-2-(5-phenyl(2-thienyl))ethyl]-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide as a white solid.

Following the procedure of Example 15, (2R)-N-[(1S)-1-(N-indan-2-ylcarbamoyl)-2-(5-phenyl(2-thienyl))ethyl]-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide (351mg, 0.43mmol) and 4/1 (v/v) mixture of trifluoroacetic acid and trimethylsilyl bromide. The crude product was purified by silica gel chromatography (water/methanol, 30:80) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-1-(N-indan-2-ylcarbamoyl)-2-(5-phenyl(2-thienyl))ethyl]hexanamide (20mg) in 9% yield, $R_f = 0.74$ (methanol/ethyl acetate, 1:9). MS $(M+H)^+$534.

Example 69: Compound 45: 2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-{[N-benzylcarbamoyl](4-phenylphenyl)methyl}pentanamide

Prepared in a manner similar to that described in Example 7 using 2.00g (6.10mmol) of 2-[(tert-butoxy)carbonylamino]-2-(4-phenylphenyl)acetic acid, 0.67mL (6.10mmol) of benzylamine, 0.826g (6.10mmol) of HOBt, 2.342g (12.20mmol) of EDC, and 1.34mL (12.20mmol) of NMM to yield 2.544g (99%) of 2-[(tert-butoxy)carbonylamino]-N-benzyl-2-(4-phenylphenyl)acetamide. MS $(M+HCO_2^-)^-$ 461.

Prepared in a manner similar to that described in Example 4 using 2.544g (6.10mmol) of 2-[(tert-butoxy)carbonylamino]-N-benzyl-2-(4-phenylphenyl)acetamide, and 25mL of 4M solution of HCl in 1,4-dioxane to yield 2.024g (94%) of 2-amino-N-benzyl-2-(4-phenylphenyl)acetamide, hydrochloride.

Prepared in a manner similar to that described in Example 24 using 0.523g (1.48mmol) of 2-amino-N-benzyl-2-(4-phenylphenyl)acetamide, hydrochloride, 0.300g (1.48mmol) of (2R)-2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.200g (1.48mmol) of HOBt, 0.569g (2.97mmol) of EDC, and 0.49mL (4.45mmol) of NMM to yield 0.700g (94%) of ethyl (3R)-3-(N-{(1S,R)[N-benzylcarbamoyl](4-phenylphenyl)methyl}carbamoyl)-5-methylhexanoate (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 501; $(M+HCO_2^-)^-$ 545.

Prepared in a manner similar to that described in Example 29 using 0.122g (0.24mmol) of ethyl (3R)-3-(N-{(1S,R)[N-benzylcarbamoyl](4-phenylphenyl)methyl}carbamoyl)-5-methylhexanoate (7:3 mixture of diastereoisomers) to yield 0.108g (92%) of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S,R)[N-benzylcarbamoyl](4-phenylphenyl) methyl}-4-methylpentanamide (7:3 mixture of diastereoisomers).
MS $(M+H)^+$ 488; $(M-H)^-$ 486.

Example 70: Compound 46: 2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-{[N-benzylcarbamoyl](3-phenylphenyl)methyl}pentanamide

Prepared in a manner similar to that described in Example 1 using 0.273g (1.5mmol) of 3-phenylbenzaldehyde, 0.303g (1.5mmol) of (2R)-2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.182mL (1.5mmol) of benzyl isocyanide and 1.5mL (3.0mmol) of 2M solution of ammonia in methanol to yield 0.572g (76%) of ethyl (3R)-3-(N-{(1S,R)[N-benzylcarbamoyl](3-phenylphenyl)methyl}carbamoyl)-5-methylhexanoate (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 501.

Prepared in a manner similar to that described in Example 29 using 0.286g (0.57mmol) of ethyl (3R)-3-(N-{(1S,R)[N-benzylcarbamoyl](3-phenylphenyl)methyl}carbamoyl)-5-methylhexanoate to yield 0.264g (95%) of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S,R)[N-benzylcarbamoyl](3-phenylphenyl)methyl}-4-methylpentanamide (3:2 mixture of diastereoisomers). MS $(M+H)^+$ 488; $(M-H)^-$ 486.

Example 71: Compound 47: 2-(N-hydroxycarbamoylmethyl)-N-(2-indol-3-ylethyl)-4-methyl-N-methylpentanamide

Prepared in a manner similar to that described in Example 24 using 0.150g (0.74mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.129g (0.74mmol) of (2-indol-3-ylethyl)methylamine, 0.100g (0.74mmol) of HOBt, 0.284g (1.48mmol) of EDC, and 0.16mL (1.48mmol) of NMM to yield 0.228g (86%) of ethyl 3-[N-(2-indol-3-ylethyl)-N-methylcarbamoyl]-5-methylhexanoate. MS $(M+H)^+$ 359; $(M+HCO_2^-)^-$ 403.

Prepared in a manner similar to that described in Example 29 using 0.228g (0.64mmol) of ethyl 3-[N-(2-indol-3-ylethyl)-N-methylcarbamoyl]-5-methylhexanoate to yield 0.088g (40%) of 2-(N-hydroxycarbamoylmethyl)-N-(2-indol-3-ylethyl)-4-methyl-N-methylpentanamide. MS $(M+H)^+$ 346; $(M-H)^-$ 344.

Example 72: Compound 48: 2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-1-(N-{(1S)-2-cyclohexyl-1-[N-(2-methoxyethyl)carbamoyl]ethyl}carbamoyl)-2-benzo[b]thiophen-3-ylethyl]hexanamide

Following the procedure of Example 3, (2S)-2-amino-3-cyclohexyl-N-(2-methoxyethyl) propanamide hydrochloride (315mg, 1.18mmol), Boc-L-3-benzothienylala (379mg, 1.18mmol), EDC (455mg, 2.37mmol), HOBt (180mg, 1.18mmol), NMM instead of DIEA (0.389mL, 3.54mmol) and dichloromethane (20mL) to yield 600mg (96%) of (2S)-2-{(2S)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino] propanoylamino}-3-cyclohexyl-N-(2-methoxyethyl)propanamide as a white solid.

Following the procedure of Example 4, (2S)-2-{(2S)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]propanoylamino}-3-cyclohexyl-N-(2-methoxyethyl)propanamide (590mg, 1.1mmol) to yield 481mg (93%) of (2S)-N-{(1S)-2-cyclohexyl-1-[N-(2-methoxyethyl)carbamoyl]ethyl}-2-amino-3-benzo[b]thiophen-3-ylpropanamide hydrochloride as a white solid.

Following the procedure of Example 3, (2S)-N-{(1S)-2-cyclohexyl-1-[N-(2-methoxyethyl)carbamoyl]ethyl}-2-amino-3-benzo[b]thiophen-3-ylpropanamide

hydrochloride (458mg, 0.97mmol), (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy]carbamoyl}methyl)hexanoic acid, sodium salt (471mg, 0.97mmol), EDC (372mg, 1.94mmol), HOBt (148mg, 0.97mmol), NMM instead of DIEA (0.213mL, 1.94mmol) and dichloromethane (20mL) to yield 683mg (81%) of (2R)-N-[(1S)-1-(N-{(1S)-2-cyclohexyl-1-[N-(2-methoxyethyl)carbamoyl]ethyl} carbamoyl)-2-benzo[b]thiophen-3-ylethyl]-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide as a yellow solid.

Following the procedure of Example 15, (2R)-N-[(1S)-1-(N-{(1S)-2-cyclohexyl-1-[N-(2-methoxyethyl)carbamoyl]ethyl}carbamoyl)-2-benzo[b]thiophen-3-ylethyl]-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide (350mg, 0.4mmol) and 4/1 (v/v) mixture of trifluoroacetic acid and trimethylsilyl bromide. The crude product was purified by silica gel chromatography (water/methanol, 30:80) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-1-(N-{(1S)-2-cyclohexyl-1-[N-(2-methoxyethyl)carbamoyl]ethyl}carbamoyl)-2-benzo[b]thiophen-3-ylethyl]hexanamide (49mg) in 20% yield, $R_f = 0.74$ (methanol/ethyl acetate, 1:4). MS $(M+H)^+$603.

Example 73: Compound 49: 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(5-(2-thienyl)(2-thienyl))methyl]pentanamide

Prepared in a manner similar to that described in Example 24 using 0.150g (0.74mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.145g (0.74mmol) of (5-(2-thienyl) -2-thienyl)methylamine, 0.114g (0.74mmol) of HOBt, 0.284g (1.48mmol) of EDC, and 0.16mL (1.48mmol) of NMM to yield 0.196g (70%) of ethyl 5-methyl-3-{N-[(5-(2-thienyl)(2-thienyl))methyl]carbamoyl}hexanoate. MS $(M+H)^+$ 380; $(M+HCO_2^-)^-$ 424.

Prepared in a manner similar to that described in Example 29 using 0.196g (0.52mmol) of ethyl 5-methyl-3-{N-[(5-(2-thienyl)(2-thienyl))methyl]carbamoyl}hexanoate to yield 0.160g (84%) of 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(5-(2-thienyl)(2-thienyl)) methyl]pentanamide. MS $(M+H)^+$ 367; $(M-H)^-$ 365.

Example 74: Compound 50: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-[4-(3-methoxyphenyl)phenyl]ethyl}-4-methylpentanamide

Following the procedure of Example 22, (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-3-(4-bromophenyl)propanamide (392mg, 1mmol), 3-methoxyphenylboronic acid (151mg , 1mmol), bis(triphenylphosphine) palladium dichloride (35mg 0.05mmol), 1M sodiumcarbonate solution (3mL) and acetonitrile (2mL) to yield 128mg (33%) of N-((1R)-1-carbamoyl-3-methylbutyl)(2S)-2-amino-3-[4-(3-methoxyphenyl)phenyl] propanamide as a yellowish brown solid.

Following the procedure of Example 3, N-((1R)-1-carbamoyl-3-methylbutyl)(2S)-2-amino-3-[4-(3-methoxyphenyl)phenyl]propanamide (108mg, 0.28mmol), (2R)-2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid (57mg, 0.28mmol), EDC (108mg, 0.56mmol), HOBt (43mg, 0.28mmol), NMM instead of DIEA (0.062mL, 0.56mmol) and dichloromethane (10mL) to yield 151mg (95%) of ethyl (3R)-3-(N-{(1R)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-[4-(3-methoxyphenyl)phenyl]ethyl}carbamoyl)-5-methylhexanoate as a yellow solid.

Using the procedure of Example 2, ethyl (3R)-3-(N-{(1R)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-[4-(3-methoxyphenyl)phenyl]ethyl}carbamoyl)-5-methylhexanoate (130mg, 0.23mmol). The crude product was purified by silica gel chromatography (water/methanol, 30:70) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-2-[4-(3-methoxyphenyl)phenyl]ethyl}-4-methylpentanamide (39mg) in 31% yield, $R_f = 0.58$ (methanol/ ethyl acetate, 1:4). MS $(M+H)^+$555.

Example 75: Compound 51: 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-(2-oxo-2-(1,2,3,4-tetrahydrobeta-carbolin-2-yl)ethyl)pentanamide

(tert-butoxy)-N-(2-oxo-2-(1,2,3,4-tetrahydrobeta-carbolin-2-yl)ethyl)carboxamide was prepared from Boc-glycine (0.875g, 5mmol), 1,2,3,4-tetrahydro-9h-pyrido[3,4-b]indole

(0.86g, 5mmol), EDC HCl (1.92g, 5mmol), HOBt (0.675g, 5mmol), DIEA (1.74mL, 10mmol) and dichloromethane (20mL) using the procedure from Example 3.
Yield: 1.55g (94%).

2-amino-1-(1,2,3,4-tetrahydrobeta-carbolin-2-yl)ethan-1-one was prepared from (tert-butoxy)-N-(2-oxo-2-(1,2,3,4-tetrahydrobeta-carbolin-2-yl)ethyl)carboxamide (0.66g, 2mmol) and 4N HCl/Dioxane using the procedure from Example 4.
Yield: 390mg (85%).

Ethyl 5-methyl-3-[N-(2-oxo-2-(1,2,3,4-tetrahydrobeta-carbolin-2-yl)ethyl)carbamoyl] hexanoate was prepared from 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid (202mg, 1mmol), 2-amino-1-(1,2,3,4-tetrahydrobeta-carbolin-2-yl)ethan-1-one (229mg, 1mmol), EDC HCl (384mg, 2mmol), HOBt (135mg, 1mmol), DIEA (358μL, 2mmol) and dichloromethane (10mL). Using the procedure from Example 3.
Yield: 380mg (92%)>

2-(N-hydroxycarbamoylmethyl)-4-methyl-N-(2-oxo-2-(1,2,3,4-tetrahydrobeta-carbolin-2-yl)ethyl)pentanamide was prepared from ethyl 5-methyl-3-[N-(2-oxo-2-(1,2,3,4-tetra hydrobeta-carbolin-2-yl)ethyl)carbamoyl] hexanoate (207mg, 0.5mmol) using the procedure from Example 2. Yield: 50mg (13%). MS: $(M+H^+)$ 401.

Example 76: Compound 52: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-[4-(4-methoxyphenyl)phenyl]ethyl}-4-methylpentanamide

Following the procedure of Example 22, (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-3-(4-bromophenyl)propanamide (392mg, 1mmol), 4-methoxyphenylboronic acid (151mg , 1mmol), bis(triphenylphosphine) palladium dichloride (35mg, 0.05mmol), 1M sodiumcarbonate solution (3mL) and acetonitrile (2mL) to yield 234mg (61%) of (2S)-2-amino-N-(1-carbamoyl-3-methylbutyl)-3-[4-(4-methoxyphenyl)phenyl]propanamide as a yellow solid.

Following the procedure of Example 3, (2S)-2-amino-N-(1-carbamoyl-3-methylbutyl)-3-[4-(4-methoxyphenyl)phenyl]propanamide (200mg, 0.52mmol), (2R)-2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid (105mg, 0.52mmol), EDC (200mg, 1.04mmol), HOBt (80mg, 0.52mmol), NMM instead of DIEA (0.114mL, 1.04mmol) and dichloromethane (10mL) to yield 191mg (66%) of ethyl (3R)-3-(N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-[4-(4-methoxyphenyl)phenyl]ethyl}carbamoyl)-5-methylhexanoate as a yellow solid.

Using the procedure of Example 2, ethyl (3R)-3-(N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-[4-(4-methoxyphenyl)phenyl]ethyl}carbamoyl)-5-methylhexanoate (160mg, 0.28mmol). The crude product was purified by hot isopropanol to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-[4-(4-methoxyphenyl) phenyl]ethyl}-4-methylpentanamide (94mg) in 61% yield, $R_f = 0.68$ (methanol/ ethyl acetate, 1:4). MS $(M+H)^+$555.

Example 77: Compound 53: 2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-2-benzo[b]thiophen-3-yl-1-(N-indan-2-ylcarbamoyl)ethyl]hexanamide

Following the procedure of Example 3, 2-aminoindan (2.07g, 15mmol), Boc-l-3-benzothienylala (5g, 15mmol), EDC (5.8g, 30mmol), HOBt (2.3g, 15mmol), NMM instead of DIEA (3.3mL, 30mmol) and dichloromethane (75mL) to yield 5.7g (87%) of (2S)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]-N-indan-2-ylpropanamide as a white solid.

Following the procedure of Example 4, (2S)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]-N-indan-2-ylpropanamide (5.8mg, 13.3mmol) to yield 4.9g (99%) of (2S)-2-amino-3-benzo[b]thiophen-3-yl-N-indan-2-ylpropanamide hydrochloride as an off white solid.

Following the procedure of Example 3, (2S)-2-amino-3-benzo[b]thiophen-3-yl-N-indan-2-ylpropanamide hydrochloride (2.8g, 7.4mmol), (2R)-2-[(ethoxycarbonyl)methyl] hexanoic acid (1.4g, 6.7mmol), EDC (2.6g, 13.5mmol), HOBt (1.03g, 6.7mmol), NMM instead of DIEA (2.3mL, 21mmol) and dichloromethane (40mL) to yield 2.09g(60%) of ethyl (3R)-3-{N-[(1S)-2-benzo[b]thiophen-3-yl-1-(N-indan-2-ylcarbamoyl)ethyl] carbamoyl}heptanoate as an off white solid.

Using the procedure of Example 2, ethyl (3R)-3-{N-[(1S)-2-benzo[b]thiophen-3-yl-1-(N-indan-2-ylcarbamoyl)ethyl]carbamoyl}heptanoate (2g, 3.84mmol). The crude product was purified by heating in methanol then acetonitrile to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-2-benzo[b]thiophen-3-yl-1-(N-indan-2-ylcarbamoyl)ethyl]hexanamide (786mg) in 40% yield.
R_f = 0.71 (methanol/ethyl acetate, 1:4). MS $(M+H)^-$ 506.

Example 78: Compound 54:
2-(N-hydroxycarbamoylmethyl)(2R)-N-((1R){N-[(1S)-2-methoxy-1-benzylethyl]carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide

Prepared in a manner similar to that described in Example 7 using 1.785g (5.45mmol) of 2-[(tert-butoxy)carbonylamino]-2-(4-phenylphenyl)acetic acid, 1.100g (5.45mmol) of (2S)-1-methoxy-3-phenylprop-2-ylamine, hydrochloride, 0.737g (5.45mmol) of HOBt, 2.091g (10.91mmol) of EDC, and 1.80mL (16.40mmol) of NMM to yield 2.401g (93%) of (2R,S)-N-[(1S)-2-methoxy-1-benzylethyl]-2-[(tert-butoxy)carbonylamino]-2-(4-phenylphenyl)acetamide (1:1 mixture of diastereoisomers).

The mixture of diastereoisomers was purified by flash chromatography (MeOH / CH_2Cl_2) to give 0.705g of (2S)-N-[(1S)-2-methoxy-1-benzylethyl]-2-[(tert-butoxy)carbonylamino]-2-(4-phenylphenyl)acetamide, R_f = 0.33 (solvent: hexanes / ethyl acetate, 2/1), and 0.810g of (2R)-N-[(1S)-2-methoxy-1-benzylethyl]-2-[(tert-butoxy)carbonylamino]-2-(4-phenylphenyl)acetamide, R_f = 0.28 (solvent: hexanes / ethyl acetate, 2/1). MS $(M+H)^+$ 475; $(M+HCO_2^-)^-$ 519.

Prepared in a manner similar to that described in Example 4 using 0.500g (1.05mmol) of (2R)-N-[(1S)-2-methoxy-1-benzylethyl]-2-[(tert-butoxy)carbonylamino]-2-(4-phenylphenyl)acetamide, and 12mL of 4M solution of HCl in 1,4-dioxane to yield 0.402g (93%) of (2R)-N-[(1S)-2-methoxy-1-benzylethyl]-2-amino-2-(4-phenylphenyl) acetamide, hydrochloride.

Prepared in a manner similar to that described in Example 24 using 0.244g (0.59mmol) of (2R)-N-[(1S)-2-methoxy-1-benzylethyl]-2-amino-2-(4-phenylphenyl)acetamide, hydrochloride, 0.120g (0.59mmol) of (2R)-2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.080g (0.59mmol) of HOBt, 0.227g (1.19mmol) of EDC, and 0.20mL (1.78mmol) of NMM to yield 0.256g (78%) of ethyl (3R)-3-[N-((1R){N-[(1S)-2-methoxy-1-benzylethyl]carbamoyl}(4-phenylphenyl)methyl)carbamoyl]-5-methylhexanoate. MS $(M+H)^+$ 559.

Prepared in a manner similar to that described in Example 29 using 0.166g (0.30mmol) of ethyl (3R)-3-[N-((1R){N-[(1S)-2-methoxy-1-benzylethyl]carbamoyl}(4-phenylphenyl) methyl)carbamoyl]-5-methylhexanoate to yield 0.110g (67%) of 2-(N-hydroxycarbamoylmethyl)(2R)-N-((1R){N-[(1S)-2-methoxy-1-benzylethyl] carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide.
MS $(M+H)^+$ 546; $(M-H)^-$ 544.

Example 79: Compound 55:
2-(N-hydroxycarbamoylmethyl)(2R)-N-((1S){N-[(1S)-2-methoxy-1-benzylethyl]carbamoyl}(4-phenylphenyl)methyl)hexanamide

Prepared in a manner similar to that described in Example 4 using 0.500g (1.05mmol) of (2S)-N-[(1S)-2-methoxy-1-benzylethyl]-2-[(tert-butoxy)carbonylamino]-2-(4-phenylphenyl)acetamide (from Compound 54), and 12mL of 4M solution of HCl in 1,4-dioxane to yield 0.423g (98%) of (2S)-N-[(1S)-2-methoxy-1-benzylethyl]-2-amino-2-(4-phenylphenyl)acetamide, hydrochloride.

Prepared in a manner similar to that described in Example 24 using 0.183g (0.44mmol) of (2S)-N-[(1S)-2-methoxy-1-benzylethyl]-2-amino-2-(4-phenylphenyl)acetamide, hydrochloride, 0.090g (0.44mmol) of (2R)-2-[(ethoxycarbonyl)methyl]hexanoic acid, 0.060g (0.44mmol) of HOBt, 0.171g (0.88mmol) of EDC, and 0.15mL (1.33mmol) of NMM to yield 0.212g (86%) of ethyl (3R)-3-[N-((1S){N-[(1S)-2-methoxy-1-benzylethyl] carbamoyl}(4-phenylphenyl)methyl)carbamoyl]heptanoate.
MS $(M+H)^+$ 559; $(M+HCO_2^-)^-$ 603.

Prepared in a manner similar to that described in Example 29 using 0.142g (0.25mmol) of ethyl (3R)-3-[N-((1S){N-[(1S)-2-methoxy-1-benzylethyl]carbamoyl}(4-phenylphenyl) methyl)carbamoyl]heptanoate to yield 0.128g (94%) of 2-(N-hydroxycarbamoylmethyl) (2R)-N-((1S){N-[(1S)-2-methoxy-1-benzylethyl]carbamoyl}(4-phenylphenyl)methyl) hexanamide. MS $(M+H)^+$ 546; $(M-H)^-$ 544.

Example 80: Compound 56: 2-(N-hydroxycarbamoylmethyl)-N-{[4-(3-methoxyphenyl)phenyl]methyl}-4-methylpentanamide

Prepared in a manner similar to that described in Example 22 using 0.152g (1.0mmol) of 3-methoxyphenylboronic acid, 0.186g (1.0mmol) of 4-bromobenzylamine, 0.035g (0.05mmol) of $Pd(PPh_3)_2Cl_2$, 2mL of 1M Na_2CO_3, and 2mL of MeCN to yield 0.210g (98%) of [4-(3-methoxyphenyl)phenyl]methylamine.

Prepared in a manner similar to that described in Example 24 using 0.120g (0.59mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.127g (0.74mmol) of [4-(3-methoxyphenyl)phenyl]methylamine, 0.080g (0.59mmol) of HOBt, 0.227g (1.19mmol) of EDC, and 0.13mL (1.19mmol) of NMM to yield 0.148g (63%) of ethyl 3-(N-{[4-(3-methoxyphenyl)phenyl]methyl}carbamoyl)-5-methylhexanoate.
MS $(M+H)^+$ 398; $(M+HCO_2^-)^-$ 442.

Prepared in a manner similar to that described in Example 29 using 0.148g (0.37mmol) of ethyl 3-(N-{[4-(3-methoxyphenyl)phenyl]methyl}carbamoyl)-5-methylhexanoate to yield

0.114g (80%) of 2-(N-hydroxycarbamoylmethyl)-N-{[4-(3-methoxyphenyl)phenyl] methyl}-4-methylpentanamide. MS $(M+H)^+$ 385; $(M-H)^-$ 383.

Example 81: Compound 57: 2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-1-(N-{(1S)-1-[N-(2-methoxyethyl)carbamoyl]-2-phenylethyl}carbamoyl)-2-benzo[b]thiophen-3-ylethyl]hexanamide

Following the procedure of Example 3, 2-methoxyethylamine (1.31mL, 15mmol), Boc-Phe-OH (3.98g, 15mmol), EDC (5.8g, 30mmol), HOBt (2.3g, 15mmol), NMM instead of DIEA (3.3mL, 30mmol) and dichloromethane (50mL) to yield 1.9g (40%) of 2-[(tert-butoxy)carbonylamino]-N-(2-methoxyethyl)-3-phenylpropanamide as a white solid.

Following the procedure of Example 4, 2-[(tert-butoxy)carbonylamino]-N-(2-methoxyethyl)-3-phenylpropanamide (1.9g, 6mmol) to yield 1.9g (99%) of 2-amino-N-(2-methoxyethyl)-3-phenylpropanamide as an off white solid.

Following the procedure of Example 3, 2-amino-N-(2-methoxyethyl)-3-phenylpropanamide (1.9g, 6mmol), Boc-l-3-benzothienylala (1.6g, 5mmol), EDC (1.9g, 10mmol), HOBt (675mg, 5mmol), NMM instead of DIEA (1.8mL, 16mmol) and dichloromethane (50mL) to yield 2.3g (88%) of (2S)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]-N-{1-[N-(2-methoxyethyl)carbamoyl]-2-phenylethyl} propanamide as a white solid.

Following the procedure of Example 4, (2S)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy) carbonylamino]-N-{1-[N-(2-methoxyethyl)carbamoyl]-2-phenylethyl} propanamide (2.2g, 4mmol) to yield 1.9g (95%) of (2S)-2-amino-3-benzo[b]thiophen-3-yl-N-{1-[N-(2-methoxyethyl)carbamoyl]-2-phenylethyl}propanamide, chloride as an off white solid.

Following the procedure of Example 3, (2S)-2-amino-3-benzo[b]thiophen-3-yl-N-{1-[N-(2-methoxyethyl)carbamoyl]-2-phenylethyl}propanamide, chloride (508mg, 1.1mmol), (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy]carbamoyl} methyl)hexanoic acid, sodium salt (438mg, 0.91mmol), EDC (346mg, 1.8mmol), HOBt

(123mg, 0.91mmol), NMM instead of DIEA (0.21mL, 1.91mmol) and dichloromethane (20mL) to yield 703mg (89%) of (2R)-N-[(1S)-2-benzo[b]thiophen-3-yl-1-(N-{1-[N-(2-methoxyethyl)carbamoyl]-2-phenylethyl}carbamoyl)ethyl]-N'-[(2,4-dimethoxyphenyl) methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide as a yellow solid.

Following the procedure of Example 15, (2R)-N-[(1S)-2-benzo[b]thiophen-3-yl-1-(N-{1-[N-(2-methoxyethyl)carbamoyl]-2-phenylethyl}carbamoyl)ethyl]-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide (350mg, 0.35mmol) and 4/1 (v/v) mixture of trifluoroacetic acid and trimethylsilyl bromide to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-1-(N-{(1S)-1-[N-(2-methoxyethyl)carbamoyl]-2-phenylethyl}carbamoyl)-2-benzo[b]thiophen-3-ylethyl]hexanamide (29mg) in 14% yield, $R_f = 0.67$ (methanol/ethyl acetate, 1:4). MS $(M+H)^+$597.

Example 82: Compound 58: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{1-[N-((1R)-1-carbamoyl-2-phenylethyl)carbamoyl](1S)-2-benzo[b]thiophen-3-ylethyl}hexanamide

Following the procedure of Compound 39, Boc-l-3-benzothienylala (1.2g, 4mmol), H-D-Phe-NH_2 (984mg, 6mmol), EDC (1.54g, 8mmol), HOBt (612mg, 4mmol), NMM instead of DIEA (1.3mL, 8mmol) and DMF (20mL) to yield 1.7g (92%) of N-((1R)-1-carbamoyl-2-phenylethyl)(2S)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino] propanamide as an off white solid.

Following the procedure of Example 4, N-((1R)-1-carbamoyl-2-phenylethyl)(2S)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]propanamide (1.8g, 3.9mmol) to yield 1.5g (99%) of N-((1R)-1-carbamoyl-2-phenylethyl)(2S)-2-amino-3-benzo[b]thiophen-3-ylpropanamide hydrochloride as a yellow solid.

Following the procedure of Example 3, N-((1R)-1-carbamoyl-2-phenylethyl)(2S)-2-amino-3-benzo[b]thiophen-3-ylpropanamide hydrochloride (367mg, 1mmol), (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy]carbamoyl}

methyl)hexanoic acid, sodium salt (481mg, 1mmol), EDC (384mg, 2mmol), HOBt (153mg, 1mmol), NMM instead of DIEA (0.22mL, 2mmol) and dichloromethane (20mL) to yield 573mg (71%) of (2R)-N-{1-[N-((1R)-1-carbamoyl-2-phenylethyl)carbamoyl] (1S)-2-benzo[b]thiophen-3-ylethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide as a yellow solid.

Following the procedure of Example 15, (2R)-N-{1-[N-((1R)-1-carbamoyl-2-phenylethyl)carbamoyl](1S)-2-benzo[b]thiophen-3-ylethyl}-N'-[(2,4-dimethoxyphenyl) methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide (373mg, 0.46mmol) and 4/1 (v/v) mixture of trifluoroacetic acid and trimethylsilyl bromide. The crude product was purified by silica gel chromatography (water/methanol, 30:70) then by prep tlc (ethyl acetate/ methanol, 10:1) to the isolation of 2-(N-hydroxycarbamoylmethyl) (2R)-N-{1-[N-((1R)-1-carbamoyl-2-phenylethyl)carbamoyl](1S)-2-benzo[b]thiophen-3-ylethyl}hexanamide (6mg) in 2% yield, $R_f = 0.58$ (methanol/ethyl acetate, 1:4).
MS $(M+H)^+$ 537.

Example 83: Compound 59: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{1-[N-((1R)-1-carbamoyl-2-phenylethyl)carbamoyl](1S)-2-benzo[b]thiophen-3-ylethyl}-4-methylpentanamide

Following the procedure of Example 3, N-((1R)-1-carbamoyl-2-phenylethyl)(2S)-2-amino-3-benzo[b]thiophen-3-ylpropanamide hydrochloride (367mg, 1mmol), (2R)-2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid (202mg, 1mmol), EDC (384mg, 2mmol), HOBt (153mg, 1mmol), NMM instead of DIEA (0.33mL, 3mmol) and dichloromethane (15mL) to yield 214mg (39%) of ethyl (3R)-3-(N-{1-[N-((1R)-1-carbamoyl-2-phenylethyl)carbamoyl](1S)-2-benzo[b]thiophen-3-ylethyl}carbamoyl)-5-methylhexanoate as a yellow solid.

Using the procedure of Example 2, ethyl (3R)-3-(N-{1-[N-((1R)-1-carbamoyl-2-phenylethyl)carbamoyl](1S)-2-benzo[b]thiophen-3-ylethyl}carbamoyl)-5-methylhexanoate (215mg, 0.28mmol). The crude product was purified by silica gel chromatography (water/methanol, 30:70) to the isolation of 2-(N-

hydroxycarbamoylmethyl)(2R)-N-{1-[N-((1R)-1-carbamoyl-2-phenylethyl)carbamoyl](1S)-2-benzo[b]thiophen-3-ylethyl}-4-methylpentanamide (41mg) in 27% yield. R_f = 0.54 (methanol/ethyl acetate, 1:4). MS $(M+H)^+$537.

Example 84: Compound 60:
2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-2-[(2S)-2-(N,N-dimethylcarbamoyl) pyrrolidinyl]-1-(benzo[b]thiophen-3-ylmethyl)-2-oxoethyl}hexanamide

N-{(1S)-2-[(2S)-2-(N,N-dimethylcarbamoyl)pyrrolidinyl]-1-(benzo[b]thiophen-3-ylmethyl)-2-oxoethyl}(tert-butoxy)carboxamide was prepared from (2S)-3-benzo[b] thiophen-3-yl-2-[(tert-butoxy)carbonylamino]propanoic acid (1.28g, 4mmol), ((2S)pyrrolidin-2-yl)-N,N-dimethylcarboxamide (0.71g, 5mmol), EDC HCl (1.54g, 8mmol), HOBt (540mg, 4mmol), DIEA (1.39mL, 8mmol), and dichloromethane using the procedure from Example 3. Yield: 1.5g (84%).

[(2S)-1-((2S)-2-amino-3-benzo[b]thiophen-3-ylpropanoyl)pyrrolidin-2-yl]-N,N-dimethylcarboxamide hydrochloride was prepared from N-{(1S)-2-[(2S)-2-(N,N-dimethyl carbamoyl) pyrrolidinyl]-1-(benzo[b]thiophen-3-ylmethyl)-2-oxoethyl}(tert-butoxy) carboxamide (0.9g, 2mmol) and 4N HCl/dioxane (10mL) using the procedure from Example 4. Yield: 680mg (89%).

(2R)-N-{(1S)-2-[(2S)-2-(N,N-dimethylcarbamoyl)pyrrolidinyl]-1-(benzo[b]thiophen-3-ylmethyl)- 2-oxoethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxy phenyl) methoxy]butane-1,4-diamide was prepared from (2R)-2-({N-[(2,4-dimethoxy phenyl)methyl]-N-[(4-methoxyphenyl)methoxy]carbamoyl}methyl)hexanoic acid, sodium salt (0.46g, 1mmol), [(2S)-1-((2S)-2-amino-3-benzo[b]thiophen-3-ylpropanoyl) pyrrolidin-2-yl]-N,N-dimethylcarboxamide hydrochloride (420mg, 1.1mmol), EDC HCl (384mg, 2mmol), HOBt (135mg, 1mmol), DIEA (570μΛ, 3.1mmol) and dichloromethane (10mL). Yield: 490mg (62%).

2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-2-[(2S)-2-(N,N-dimethylcarbamoyl) pyrrol idinyl]-1-(benzo[b]thiophen-3-ylmethyl)-2-oxoethyl}hexanamide was prepared from (2R)-N-{(1S)-2-[(2S)-2-(N,N-dimethylcarbamoyl)pyrrolidinyl]-1-(benzo[b]thiophen-3-ylmethyl)- 2-oxoethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxy phenyl) methoxy]butane-1,4-diamide (0.393g, 0.5mmol) using the procedure from Example 15. Yield: 0.9g (69%). MS: ($M+H^+$) 517.

Example 85: Compound 61: 2-(N-hydroxycarbamoylmethyl)-N-{2-[4-(4-methoxyphenyl)phenyl]ethyl}-4-methylpentanamide

2-[4-(3-methoxyphenyl)phenyl]ethylamine was prepared from 2-phenylethylamine (310μL, 2mmol), 4-methoxyphenyl boronic acid (310mg, 2mmol), bis(triphenylphosphine) palladium dichloride (70mg 0.1mmol), 1M sodiumcarbonate solution (6mL) and acetonitrile (4mL) using the procedure from Example 22. Yield: 230mg, (50%).

Ethyl 3-(N-{2-[4-(4-methoxyphenyl)phenyl]ethyl}carbamoyl)-5-methylhexanoate from 2-[(ethoxycarbonyl) methyl]- 4-methylpentanoic acid (94mg 0.5mmol), 2-[4-(3-methoxyphenyl)phenyl]ethylamine (114mg, 0.5mmol), EDC HCl (192mg, 1mmol), HOBt (68mg, 0.5mmol), DIEA (184μL, 1mmol), dichloromethane (5mL) using the procedure from Example 3. Yield: 0.35g (85%).

2-(N-hydroxycarbamoylmethyl)-N-{2-[4-(4-methoxyphenyl)phenyl]ethyl}-4-methylpentanamide was prepared from ethyl 3-(N-{2-[4-(4-methoxyphenyl) phenyl] ethyl} carbamoyl)-5-methylhexanoate (206mg, 0.5mmol), using the procedure from Example 2. Yield: 100mg (50%). MS: ($M+H^+$) 399.

Example 86: Compound 62: 2-(N-hydroxycarbamoylmethyl)-N-{2-[4-(3-methoxyphenyl)phenyl]ethyl}-4-methylpentanamide

2-[4-(3-methoxyphenyl)phenyl]ethylamine was prepared from 2-phenylethylamine (310μL, 2mmol), 3-methoxyphenylboronic acid (310mg, 2mmol),

bis(triphenylphosphine) palladium dichloride (70mg 0.1mmol), 1M sodiumcarbonate solution (6mL) and acetonitrile (4mL) using the procedure from Example 22. Yield: 340mg (75%).

Ethyl 3-(N-{2-[4-(3-methoxyphenyl)phenyl]ethyl}carbamoyl)-5-methylhexanoate was prepared from 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid (188mg, 1mmol), 2-[4-(3-methoxyphenyl)phenyl]ethylamine (227mg, 1mmol), EDC HCL (384mg, 2mmol), HOBt (135mg, 1mmol), DIEA (358μL, 2mmol) and dichlromethane (10mL) using the procedure from Example 3. Yield: 325mg (79%).

2-(N-hydroxycarbamoylmethyl)-N-{2-[4-(3-methoxyphenyl)phenyl]ethyl}-4-methylpentanamide was prepared from Ethyl 3-(N-{2-[4-(3-methoxyphenyl) phenyl] ethyl}carbamoyl)-5-methylhexanoate (70mg, 0.17mmol) using the procedure from Example 2. Yield: 100mg (50%). MS: ($M+H^+$) 399.

Example 87: Compound 63: 2-(N-hydroxycarbamoylmethyl)(2R)-N-((1S)-1-{N-[(1S)-2-oxo-1-benzyl-2-pyrrolidinylethyl]carbamoyl}-2-benzo[b]thiophen-3-ylethyl)hexanamide

Following the procedure of Example 3, Boc-l-3-benzothienylala (1.6g, 5mmol), H-Phe-pyrrolidide (1.09g, 5mmol), EDC (1.92g, 10mmol), HOBt (765mg, 5mmol), NMM instead of DIEA (1.1mL, 10mmol) and dichloromethane (20mL) to yield 2.4g (92%) of (2S)-N-[(1S)-2-oxo-1-benzyl-2-pyrrolidinylethyl]-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]propanamide as a yellow solid.

Following the procedure of Example 4, (2S)-N-[(1S)-2-oxo-1-benzyl-2-pyrrolidinylethyl]-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]propanamide (2.4g, 4.6mmol) to yield 1.9g (90%) of (2S)-N-[(1S)-2-oxo-1-benzyl-2-pyrrolidinylethyl]-2-amino-3-benzo[b]thiophen-3-ylpropanamide hydrochloride as a yellow solid.

Following the procedure of Example 3, (2S)-N-[(1S)-2-oxo-1-benzyl-2-pyrrolidinylethyl] -2-amino-3-benzo[b]thiophen-3-ylpropanamide hydrochloride (457mg, 1mmol), (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy]carbamoyl}methyl) hexanoic acid, sodium salt (48mg, 1mmol), EDC (384mg, 2mmol), HOBt (153mg, 1mmol), NMM instead of DIEA (0.22mL, 2mmol) and dichloromethane (20mL) to yield 690mg (80%) of (2R)-N-((1S)-1-{N-[(1S)-2-oxo-1-benzyl-2-pyrrolidinylethyl] carbamoyl}-2-benzo[b]thiophen-3-ylethyl)-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide as a light yellow solid.

Following the procedure of Example 15, (2R)-N-((1S)-1-{N-[(1S)-2-oxo-1-benzyl-2-pyrrolidinylethyl]carbamoyl}-2-benzo[b]thiophen-3-ylethyl)-N'-[(2,4-dimethoxyphenyl) methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide (370mg, 0.42mmol) and 4/1 (v/v) mixture of trifluoroacetic acid and trimethylsilyl bromide. The crude product was purified by silica gel chromatography (water/methanol, 30:70) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-((1S)-1-{N-[(1S)-2-oxo-1-benzyl-2-pyrrolidinylethyl]carbamoyl}-2-benzo[b]thiophen-3-ylethyl)hexanamide (24mg) in 10% yield, $R_f = 0.61$ (methanol/ethyl acetate, 1:4). MS (M+H)593.

Example 88: Compound 64:
2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-phenylethyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}hexanamide

Following the procedure of Example 3, Boc-l-3-benzothienylala (1.6g, 5mmol), H-Phe-NH_2 (820mg, 5mmol), EDC (1.92g, 10mmol), HOBt (765mg, 5mmol), NMM instead of DIEA (1.1mL, 10mmol) and dichloromethane (20mL) to yield 1.5g (65%) of (2S)-N-((1S)-1-carbamoyl-2-phenylethyl)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy) carbonylamino]propanamide as a white solid.

Following the procedure of Example 4, (2S)-N-((1S)-1-carbamoyl-2-phenylethyl)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]propanamide (1.5g, 3.2mmol) to yield 1.2g (95%) of (2S)-N-((1S)-1-carbamoyl-2-phenylethyl)-2-amino-3-benzo[b]thiophen-3-ylpropanamide hydrochloride as a white solid.

Following the procedure of Example 3, (2S)-N-((1S)-1-carbamoyl-2-phenylethyl)-2-amino-3-benzo[b]thiophen-3-ylpropanamide hydrochloride (439mg, 1.09mmol), (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl)methoxy]carbamoyl} methyl)hexanoic acid, sodium salt (526mg, 1.09mmol), EDC (419mg, 2.18mmol), HOBt (167mg, 1.09mmol), NMM instead of DIEA (0.239mL, 2.08mmol) and dichloromethane (20mL) to yield 433mg (58%) of (2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-phenylethyl) carbamoyl]-2-benzo[b]thiophen-3-ylethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide as a yellow solid.

Following the procedure of Example 15, (2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-phenylethyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}-N'-[(2,4-dimethoxyphenyl) methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide (300mg, 0.37mmol) and 4/1 (v/v) mixture of trifluoroacetic acid and trimethylsilyl bromide. The crude product was purified by silica gel chromatography (water/methanol, 30:70) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-phenylethyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}hexanamide (8mg) in 4% yield, R_f = 0.64 (methanol/ethyl acetate, 1:4). MS $(M+H)^+$539.

Example 89: Compound 65: 2-[2-(N-hydroxycarbamoylmethyl)-4-methylpentanoylamino](2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-N'-{[4-((hydroxyamino)iminomethyl)phenyl]methyl}pentane-1,5-diamide

Phenylmethyl (4S)-4-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-4-[(tert-butoxy)carbonylamino]butanoate was prepared from boc-L-glu(obzl)-acid (3.37g, 10mmol), L-leucineamide (1.43g, 11mmol), EDC HCl (3.84g, 20mmol), HOBt (1.35g, 10mmol), DIEA (3.48mL, 20mmol), DMF (25mL) using the procedure from Compound 39 using microwaves for heating. Yield: 3.8g (88%).

(4S)-4-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-4-[(tert-butoxy)carbonylamino] butanoic acid was prepared from phenylmethyl (4S)-4-[N-((1S)-1-carbamoyl-3-methyl

butyl)carbamoyl]-4-[(tert-butoxy)carbonylamino]butanoate (3.6g, 8mmol) using the procedure from Example 6. Yield: 2.7g (96%).

(2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(tert-butoxy)carbonylamino]-N'-[(4-cyano phenyl)methyl]-pentane-1,5-diamide was prepared from (4S)-4-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-4-[(tert-butoxy)carbonylamino] butanoic acid (1.795g, 5mmol), 4-cyanobenzylamine hydrochloride (1.008g, 6mmol), EDC HCl (1.92g, 10mmol), HOBt (0.765g, 5mmol), DIEA (2.78mL, 16mmol) and DMF using the procedure from Compound 39 using microwaves for heating. Yield: 0.9g, (37%).

(2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-N'-[(4-cyanophenyl)methyl]pentane-1,5-diamide was prepared from (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(tert-butoxy) carbonylamino]-N'-[(4-cyano phenyl)methyl]-pentane-1,5-diamide (475mg, 1mmol) using the procedure from Example 4. Yield: 200mg, (54%).

Ethyl 3-[N-((1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-3-{N-[(4-cyano phenyl)methyl]-carbamoyl}propyl)carbamoyl]-5-methylhexanoate was prepared from 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid (202mg, 1mmol), (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-N'-[(4-cyanophenyl)methyl]pentane-1,5-diamide (187mg, 0.5mmol), EDC HCl (384mg, 2.0mmol), HOBt (135mg, 1mmol), DIEA 348μL, 2mmol), and dichloromethane (10mL) using the procedure from Example 3. Yield: 250mg (89%).

2-[2-(N-hydroxycarbamoylmethyl)-4-methylpentanoylamino](2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-N'-{[4-((hydroxyamino) iminomethyl)phenyl]methyl}pentane-1,5-diamide was prepared from ethyl 3-[N-((1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-3-{N-[(4-cyano phenyl)methyl]-carbamoyl}propyl)carbamoyl]-5-methylhexanoate using the procedure from Example 2.
Yield: 12mg (7%). MS: ($M+H^+$) 578.

2-[4-(3-methylphenyl)phenyl]ethylamine was prepared from 4-bromophenethylamine (400mg, 2mmol), 3-tolylboronic acid (270mg, 2mmol), bis(triphenylphosphine) palladium dichloride (70mg, 0.1mmol), 1M sodiumcarbonate solution (6mL) and acetonitrile (4mL) using the procedure from Example 22. Yield: 0.2g (47%).

Ethyl 5-methyl-3-(N-{2-[4-(3-methylphenyl)phenyl]ethyl}carbamoyl)hexanoate was prepared from 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid (101mg, 0.5mmol), 2-[4-(3-methylphenyl)phenyl]ethylamine (105mg, 0.5mmol), EDC HCl (192mg, 1mmol), HOBt (67mg, 0.5mmol), DIEA (174μL, 1mmol), and dichloromethane (5mL) using the procedure in Example 3. Yield: 158mg (40%).

Example 90: Compound 66: 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-{2-[4-(3-methylphenyl)phenyl]ethyl} pentanamide

2-(N-hydroxycarbamoylmethyl)-4-methyl-N-{2-[4-(3-methylphenyl)phenyl]ethyl} pentanamide was prepared from Ethyl 5-methyl-3-(N-{2-[4-(3-methylphenyl) phenyl] ethyl}carbamoyl)hexanoate (115mg, 0.29mmol) using the procedure from Example 2. Yield: 20mg, (18%). MS: $(M+H^+)$ 383.

Example 91: Compound 67: 2-(N-hydroxycarbamoylmethyl)-N-{(1S)-2-benzo[b]thiophen-3-yl-1-[N-(2-(2H-3,4,5,6-tetrahydropyran-4-yl)ethyl)carbamoyl]ethyl}-4-methylpentanamide

Following the procedure of Example 3, Boc-l-3-benzothienylala (321mg, 1mmol), 4-(2-aminoethyl)tetrahydropyran hydrochloride (165mg, 1mmol), EDC (384mg, 2mmol), HOBt (153mg, 1mmol), NMM instead of DIEA (0.329mL, 3mmol) and dichloromethane (10mL) to yield 369mg (65%) of N-(2-(2H-3,4,5,6-tetrahydropyran-4-yl)ethyl)(2S)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]propanamide as a yellow solid.

Following the procedure of Example 4, N-(2-(2H-3,4,5,6-tetrahydropyran-4-yl)ethyl) (2S)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]propanamide (305mg, 0.7mmol) to yield 227mg (88%) of N-(2-(2H-3,4,5,6-tetrahydropyran-4-yl)ethyl)(2S)-2-amino-3-benzo[b]thiophen-3-ylpropanamide hydrochloride as a yellow solid.

Following the procedure of Example 3, 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid (110mg, 0.54mmol), N-(2-(2H-3,4,5,6-tetrahydropyran-4-yl)ethyl)(2S)-2-amino-3-benzo[b]thiophen-3-ylpropanamide hydrochloride (200mg, 0.54mmol), EDC (207mg, 1.08mmol), HOBt (83mg, 0.54mmol), NMM instead of DIEA (0.177mL, 1.62mmol) and dichloromethane (10mL) to yield 109mg (38%) of methyl 3-(N-{(1S)-2-benzo[b]thiophen-3-yl-1-[N-(2-(2H-3,4,5,6-tetrahydropyran-4-yl)ethyl)carbamoyl] ethyl}carbamoyl)-5-methylhexanoate as a yellow solid.

Using the procedure of Example 2, methyl 3-(N-{(1S)-2-benzo[b]thiophen-3-yl-1-[N-(2-(2H-3,4,5,6-tetrahydropyran-4-yl)ethyl)carbamoyl]ethyl}carbamoyl)-5-methylhexanoate (108mg, 0.21mmol). The crude product was purified by silica gel chromatography (water/methanol, 30:70) to the isolation of 2-(N-hydroxycarbamoylmethyl)-N-{(1S)-2-benzo[b]thiophen-3-yl-1-[N-(2-(2H-3,4,5,6-tetrahydropyran-4-yl)ethyl)carbamoyl] ethyl}-4-methylpentanamide (8mg) in 8% yield (more polar product), $R_f = 0.53$ (methanol/ ethyl acetate, 1:4). MS $(M+H)^+$504.

Example 92: Compound 68: 2-(N-hydroxycarbamoylmethyl)-N-[(2,3-dimethylindol-5-yl)methyl]-4-methylpentanamide

Prepared in a manner similar to that described in Example 24 using 0.126g (0.62mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.109g (0.62mmol) of (2,3-dimethylindol-5-yl)methylamine, 0.084g (0.62mmol) of HOBt, 0.239g (1.25mmol) of EDC, and 0.14mL (1.25mmol) of NMM to yield 0.074g (33%) of ethyl 3-{N-[(2,3-dimethylindol-5-yl)methyl]carbamoyl}-5-methylhexanoate.
MS $(M+H)^+$ 359; $(M-H)^-$ 357.

Prepared in a manner similar to that described in Example 29 using 0.074g (0.21mmol) of ethyl 3-{N-[(2,3-dimethylindol-5-yl)methyl]carbamoyl}-5-methylhexanoate to yield 0.036g (50%) of 2-(N-hydroxycarbamoylmethyl)-N-[(2,3-dimethylindol-5-yl)methyl]-4-methylpentanamide. MS $(M+H)^+$ 346; $(M-H)^-$ 344.

Example 93: Compound 69: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}-4-methylpentanamide

Following the procedure of Compound 39, Boc-l-3-benzothienylala (1.6g, 5mmol), (2S)-2-amino-4-methylpentanamide (975mg, 7.5mmol), EDC (1.9g, 10mmol), HOBt (765mg, 5mmol), DIEA (1.7mL, 10mmol) and DMF (20mL) to yield 1.8g (83%) (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino] propanamide as a white solid.

Following the procedure of Example 4, (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]propanamide (1.7g, 3.9mmol) to yield 1.4g of (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-3-benzo[b]thiophen-3-ylpropanamide as a yellow solid.

Following the procedure of Example 3, (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-3-benzo[b]thiophen-3-ylpropanamide (163mg, 0.49mmol), 2-[(ethoxycarbonyl) methyl]-4-methylpentanoic acid (100mg, 0.49mmol), EDC (188mg, 0.98mmol), HOBt (75mg, 0.49mmol), DIEA (0.17mL, 0.98mmol) and dichloromethane (15mL) to yield 207mg (82%) of ethyl 3-(N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}carbamoyl)-5-methylhexanoate as a white solid.

Using the procedure of Example 2, ethyl 3-(N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}carbamoyl)-5-methylhexanoate (134mg, 0.21mmol). The crude product was purified by silica gel chromatography (water/methanol, 30:70) to the isolation of 2-(N-hydroxycarbamoylmethyl) (2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}-4-methylpentanamide (2.8mg) in 2% yield.

R_f = 0.48 (methanol/ ethyl acetate, 1:4). MS $(M+H)^+$505.

Example 94: Compound 70: 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(5-(2-pyridyl)(2-thienyl))methyl]pentanamide

Prepared in a manner similar to that described in Example 24 using 0.100g (0.49mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.130g (0.49mmol) of [5-(2-pyridinyl)-2-thienyl]methylamine dihydrochloride, 0.067g (0.49mmol) of HOBt, 0.190g (0.99mmol) of EDC, and 0.22mL (1.98mmol) of NMM to yield 0.158g (86%) of ethyl 5-methyl-3-{N-[(5-(2-pyridyl)(2-thienyl))methyl]carbamoyl}hexanoate. MS $(M+H)^+$ 375; $(M+HCO_2^-)^-$ 419.

Prepared in a manner similar to that described in Example 29 using 0.144g (0.38mmol) of ethyl 5-methyl-3-{N-[(5-(2-pyridyl)(2-thienyl))methyl]carbamoyl}hexanoate to yield 0.118g (86%) of 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(5-(2-pyridyl)(2-thienyl))methyl]pentanamide. MS $(M+H)^+$ 362; $(M-H)^-$ 360.

Example 95: Compound 71: 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(4-(2-thienyl)phenyl)methyl]pentanamide

Prepared in a manner similar to that described in Example 24 using 0.100g (0.49mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.094g (0.49mmol) of [5-(2-pyridinyl)-2-thienyl]methylamine dihydrochloride, 0.067g (0.49mmol) of HOBt, 0.190g (0.99mmol) of EDC, and 0.11mL (0.99mmol) of NMM to yield 0.152g (83%) of ethyl 5-methyl-3-{N-[(4-(2-thienyl)phenyl)methyl]carbamoyl}hexanoate.
MS $(M+H)^+$ 374; $(M+HCO_2^-)^-$ 418.

Prepared in a manner similar to that described in Example 29 using 0.116g (0.31mmol) of ethyl 5-methyl-3-{N-[(4-(2-thienyl)phenyl)methyl]carbamoyl}hexanoate to yield 0.086g (77%) of 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(4-(2-thienyl)phenyl)methyl] pentanamide. MS $(M+H)^+$ 361; $(M-H)^-$ 359.

Example 96: Compound 72: 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(4-(1,2,3-thiadiazol-4-yl)phenyl)methyl]pentanamide

Prepared in a manner similar to that described in Example 24 using 0.100g (0.49mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.113g (0.49mmol) of 4-(1,2,3-thiadiazol-4-yl)benzylamine hydrochloride, 0.067g (0.49mmol) of HOBt, 0.190g (0.99mmol) of EDC, and 0.16mL (1.48mmol) of NMM to yield 0.178g (97%) of ethyl 5-methyl-3-{N-[(4-(1,2,3-thiadiazol-4-yl)phenyl)methyl]carbamoyl}hexanoate. MS $(M+H)^+$ 376; $(M+HCO_2^-)^-$ 420.

Prepared in a manner similar to that described in Example 29 using 0.148g (0.39mmol) of ethyl 5-methyl-3-{N-[(4-(1,2,3-thiadiazol-4-yl)phenyl)methyl]carbamoyl}hexanoate to yield 0.121g (86%) of 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(4-(1,2,3-thiadiazol-4-yl)phenyl)methyl]pentanamide. MS $(M+H)^+$ 363; $(M-H)^-$ 361.

Example 97: Compound 73: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}hexanamide

Following the procedure of Example 3, 2-[(tert-butoxy)carbonylaminooxy]acetic acid (333mg, 1mmol), (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl) methoxy]carbamoyl}methyl)hexanoic acid, sodium salt (481mg, 1mmol), EDC (384mg, 2mmol), HOBt (153mg, 1mmol), DIEA (0.174mL, 1mmol) and dichloromethane (10mL) to yield 595mg (77%) of (2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-2-benzo[b]thiophen-3-ylethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide as a white solid.

Following the procedure of Example 15, (2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}-N'-[(2,4-dimethoxyphenyl) methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide (500mg, 0.65mmol) and 4/1 (v/v) mixture of trifluoroacetic acid and trimethylsilyl bromide. The crude product was purified hot methanol to the isolation of 2-(N-hydroxycarbamoylmethyl) (2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}hexanamide (26mg) in 8% yield, $R_f = 0.48$ (methanol/ethyl acetate, 1:4).
MS $(M+H)^+$.505

Compound 74: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-2-(3-phenylphenyl)ethyl}hexanamide

(2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(tert-butoxy)carbonylamino]-3-(3-bromo phenyl)propanamide was prepared from (2S)-2-[(tert-butoxy)carbonylamino]-3-(3-bromophenyl)propanoic acid (1.03g, 3mmol), (2S)-2-amino-4-methylpentanamide (0.455g, 3.5mmol), EDC HCl (1.152g, 6mmol), HOBt (0.405g, 3mmol), DIEA (1.04mL, 6mmol) and DMF (10mL) using the procedure from Compound 39.
Yield: 1.15g, (83%).

(2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-3-(3-bromophenyl)propanamide was prepared from 2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(tert-butoxy)carbonylamino]-3-(3-bromo phenyl)propanamide (1.03g, 2.25mmol) and 4N HCl/dioxane (10mL) using the procedure from Example 4. Yield: 750mg (73%).

(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-(3-bromophenyl) ethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4methoxyphenyl)methoxy] butane-1,4-diamide was prepared from (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-[(4-methoxyphenyl) methoxy]carbamoyl}methyl)hexanoic acid, sodium salt (962mg, 2mmol), (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-3-(3-bromophenyl) propanamide (712mg, 2moles), EDC HCl (768mg, 4mmol), HOBt (270mg, 2mmol), DIEA (284μL, 2mmol) and DMF (10mL) using the procedure in Compound 39.
Yield: 1.15g (72%).

(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-(3-phenylphenyl) ethyl}-N'-[(2,4-dimethoxyphenyl)-methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy] butane-1,4-diamide was prepared from (2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-(3-bromophenyl) ethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4methoxyphenyl)methoxy] butane-1,4-diamide (0.8g, 1mmol), and phenylboronic acid (214mg, 1mmol), bis(triphenylphosphine) palladium dichloride

(35mg, 0.05mmol), 1M sodiumcarbonate solution (3mL) and acetonitrile (2mL) using the procedure from Example 22. Yield: 0.4g, (50%).

2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-2-(3-phenylphenyl)ethyl}hexanamide was prepared from (2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-(3-phenylphenyl) ethyl}-N'-[(2,4-di-methoxyphenyl)-methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy] butane-1,4-diamide (250mg, 0.3mmol) using the procedure from Example 15.
Yield: 30mg (19%). MS: ($M-H^+$) 523.

Example 98: Compound 75:
3-(N-hydroxycarbamoyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-(4-phenylphenyl)ethyl}-2-methylpropanamide

Prepared in a manner similar to that described in Example 24 using 0.075g (0.51mmol) of (R)-(+)-2-methylsuccinic acid 4-methyl ester, 0.200g (0.51mmol) of (2S)-N-((1S,2S)-1-carbamoyl-2-methylbutyl)-2-amino-3-(4-phenylphenyl)propanamide hydrochloride (See Compound 86), 0.069g (0.51mmol) of HOBt, 0.197g (1.02mmol) of EDC, and 0.17mL (1.54mmol) of NMM to yield 0.222g (90%) of methyl (3R)-3-(N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-(4-phenylphenyl)ethyl}carbamoyl)butanoate.
MS $(M+H)^+$ 482; $(M+HCO_2^-)^-$ 526.

Prepared in a manner similar to that described in Example 29 using 0.222g (0.46mmol) of methyl (3R)-3-(N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-(4-phenylphenyl)ethyl}carbamoyl)butanoate to yield 0.218g (98%) of 3-(N-hydroxycarbamoyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-(4-phenylphenyl)ethyl}-2-methylpropanamide. MS $(M+H)^+$ 483; $(M-H)^-$ 481.

Example 99: Compound 76: 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(3-phenylphenyl)methyl]pentanamide

Prepared in a manner similar to that described in Example 24 using 0.120g (0.59mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.109g (0.59mmol) of 3-

phenylbenzylamine, 0.080g (0.59mmol) of HOBt, 0.227g (1.19mmol) of EDC, and 0.13mL (1.19mmol) of NMM to yield 0.192g (89%) of ethyl 5-methyl-3-{N-[(3-phenylphenyl)methyl]carbamoyl}hexanoate. MS $(M+H)^+$ 368; $(M+HCO_2^-)^-$ 412.

Prepared in a manner similar to that described in Example 29 using 0.192g (0.52mmol) of ethyl 5-methyl-3-{N-[(3-phenylphenyl)methyl]carbamoyl}hexanoate to yield 0.144g (78%) of 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(3-phenylphenyl) methyl]pentanamide. MS $(M+H)^+$ 355; $(M-H)^-$ 353.

Example 100: Compound 77: 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(4-phenylphenyl)methyl]pentanamide

Prepared in a manner similar to that described in Example 24 using 0.120g (0.59mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.109g (0.59mmol) of 4-phenylbenzylamine, 0.080g (0.59mmol) of HOBt, 0.227g (1.19mmol) of EDC, and 0.13mL (1.19mmol) of NMM to yield 0.198g (91%) of ethyl 5-methyl-3-{N-[(4-phenylphenyl)methyl]carbamoyl}hexanoate. MS $(M+H)^+$ 368; $(M+HCO_2^-)^-$ 412.

Prepared in a manner similar to that described in Example 29 using 0.132g (0.36mmol) of ethyl 5-methyl-3-{N-[(4-phenylphenyl)methyl]carbamoyl}hexanoate to yield 0.092g (72%) of 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(4-phenylphenyl)methyl] pentanamide. MS $(M+H)^+$ 355; $(M-H)^-$ 353.

Example 101: Compound 78: 2-(N-hydroxycarbamoylmethyl)(2S)-N-{(1S)-1-[N-methyl-N-benzylcarbamoyl]-2-(2-naphthyl)ethyl}-4-methylpentanamide

Prepared in a manner similar to that described in Example 24 using 1.00g (3.17mmol) of (S)-(-)-2-(tert-butoxycarbonylamino)-3-(2-naphthyl)propanoic acid, 0.384g (3.17mmol) of N-methylbenzylamine, 0.428g (3.17mmol) of HOBt, 1.216g (6.34mmol) of EDC, and 0.697mL (6.34mmol) of NMM to yield 1.220g (92%) of [1-(Benzyl-methyl-carbamoyl)-2-naphthalen-2-yl-ethyl]-carbamic acid tert-butyl ester. MS $(M+H)^+$ 419.

Prepared in a manner similar to that described in Example 4 using 1.200g (2.87mmol) of [1-(Benzyl-methyl-carbamoyl)-2-naphthalen-2-yl-ethyl]-carbamic acid tert-butyl ester, and 20mL of 4M solution of HCl in 1,4-dioxane to yield 1.005g (99%) of 1-(Benzyl-methyl-carbamoyl)-2-naphthalen-2-yl-ethyl-ammonium.

Prepared in a manner similar to that described in Example 24 using 0.386g (1.09mmol) of 1-(Benzyl-methyl-carbamoyl)-2-naphthalen-2-yl-ethyl-ammonium; chloride, 0.220g (1.09mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.147g (1.09mmol) of HOBt, 0.417g (2.18mmol) of EDC, and 0.3mL (3.26mmol) of NMM to yield 0.454g (83%) of ethyl (3R,S)-3-(N-{(1S)-1-[N-methyl-N-benzylcarbamoyl]-2-(2-naphthyl) ethyl}carbamoyl)-5-methylhexanoate (1:1 mixture of diastereoisomers).

The mixture of diastereoisomers was purified by flash chromatography (EtOAc / hexanes) to give 0.200g of ethyl (3R)-3-(N-{(1S)-1-[N-methyl-N-benzylcarbamoyl]-2-(2-naphthyl)ethyl}carbamoyl)-5-methylhexanoate, $R_f = 0.23$ (solvent: hexanes / ethyl acetate, 2/1), MS $(M+H)^+$ 503; $(M+HCO_2^-)^-$ 547; and 0.206g of ethyl (3S)-3-(N-{(1S)-1-[N-methyl-N-benzylcarbamoyl]-2-(2-naphthyl)ethyl}carbamoyl)-5-methylhexanoate, $R_f = 0.18$ (solvent: hexanes / ethyl acetate, 2/1). MS $(M+H)^+$ 503.

Prepared in a manner similar to that described in Example 29 using 0.168g (0.33mmol) of ethyl (3S)-3-(N-{(1S)-1-[N-methyl-N-benzylcarbamoyl]-2-(2-naphthyl)ethyl} carbamoyl)-5-methylhexanoate to yield 0.149g (92%) of 2-(N-hydroxycarbamoylmethyl) (2S)-N-{(1S)-1-[N-methyl-N-benzylcarbamoyl]-2-(2-naphthyl)ethyl}-4-methylpentanamide. MS $(M+H)^+$ 490; $(M-H)^-$ 488.

Example 102: Compound 79: 2-(N-hydroxycarbamoylmethyl)-N-[(1S)-2-isoindolin-2-yl-1-(2-naphthylmethyl)-2-oxoethyl]-4-methylpentanamide

Prepared in a manner similar to that described in Example 24 using 1.00g (3.17mmol) of (S)-(-)-2-(tert-butoxycarbonylamino)-3-(2-naphthyl)propanoic acid, 0.360g (3.17mmol) of isoindoline, 0.428g (3.17mmol) of HOBt, 1.216g (6.34mmol) of EDC, and 0.697mL

(6.34mmol) of NMM to yield 1.210g (91%) of [2-(1,3-Dihydro-isoindol-2-yl)-1-naphthalen-2-ylmethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester. MS $(M+H)^+$ 417.

Prepared in a manner similar to that described in Example 4 using 1.200g (2.88mmol) of [2-(1,3-Dihydro-isoindol-2-yl)-1-naphthalen-2-ylmethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester, and 20mL of 4M solution of HCl in 1,4-dioxane to yield 0.98g (96%) of 2-(1,3-Dihydro-isoindol-2-yl)-1-naphthalen-2-ylmethyl-2-oxo-ethyl-ammonium; chloride.

Prepared in a manner similar to that described in Example 24 using 0.272g (0.77mmol) of 2-(1,3-Dihydro-isoindol-2-yl)-1-naphthalen-2-ylmethyl-2-oxo-ethyl-ammonium; chloride, 0.156g (0.77mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.104g (0.77mmol) of HOBt, 0.296g (1.54mmol) of EDC, and 0.25mL (2.3mmol) of NMM to yield 0.348g (90%) of ethyl (3R,S)-3-{N-[(1S)-2-isoindolin-2-yl-1-(2-naphthylmethyl)-2-oxoethyl]carbamoyl}-5-methylhexanoate (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 501; $(M+HCO_2^-)^-$ 545.

Prepared in a manner similar to that described in Example 29 using 0.348g (0.70mmol) of ethyl (3R,S)-3-{N-[(1S)-2-isoindolin-2-yl-1-(2-naphthylmethyl)-2-oxoethyl]carbamoyl}-5-methylhexanoate (1:1 mixture of diastereoisomers) to yield 0.278g (82%) of 2-(N-hydroxycarbamoylmethyl)(2R,S)-N-[(1S)-2-isoindolin-2-yl-1-(2-naphthylmethyl)-2-oxoethyl]-4-methylpentanamide (1:1 mixture of diastereoisomers).
MS $(M+H)^+$ 488; $(M-H)^-$ 486.

Example 103: Compound 80: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-methyl-N-benzylcarbamoyl]-2-(2-naphthyl)ethyl}-4-methylpentanamide

Prepared in a manner similar to that described in Example 29 using 0.128g (0.25mmol) of ethyl (3R)-3-(N-{(1S)-1-[N-methyl-N-benzylcarbamoyl]-2-(2-naphthyl)ethyl} carbamoyl)-5-methylhexanoate (from Compound 78) to yield 0.109g (89%) of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-methyl-N-benzylcarbamoyl]-2-(2-naphthyl)ethyl}-4-methylpentanamide. MS $(M+H)^+$ 490; $(M-H)^-$ 488.

Example 104: Compound 81: 3-(N-hydroxycarbamoyl)(2S)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl}-2-(cyclobutylmethyl) propanamide and Compound 82: 3-(N-hydroxycarbamoyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl}-2-(cyclobutylmethyl) propanamide

Prepared in a manner similar to that described in Example 23 using 3.00g (9.90mmol) of tert-butyl ethyl 2-[(tert-butyl)oxycarbonyl]butane-1,4-dioate, 2.23mL (19.80mmol) of cyclobutylmethyl bromide, 0.397g (9.90mmol) of NaH to yield 3.252g (88%) of 2-tert-Butoxycarbonyl-2-cyclobutylmethyl-succinic acid 1-tert-butyl ester 4-ethyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (2H, q), 2.85 (2H, s), 2.33-2.21 (1H, m), 2.05 (2H, d), 2.03-1.99 (2H, m), 1.74-1.59 (4H, m), 1.45 (18H, s), 1.24 (3H, t).

Prepared in a manner similar to that described in Example 23 using 1.50g (4.05mmol) of 2-tert-Butoxycarbonyl-2-cyclobutylmethyl-succinic acid 1-tert-butyl ester 4-ethyl ester, 10mL of TFA to yield 1.00g (96%) of 2-Carboxy-2-cyclobutylmethyl-succinic acid 4-ethyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (2H, br s), 4.15 (2H, q), 3.09 (2H, s), 2.40-2.35 (1H, m), 2.11-2.03 (2H, m), 2.05 (2H, d), 1.90-1.61 (4H, m), 1.25 (3H, t).

Prepared in a manner similar to that described in Example 23 using 1.00g (3.87mmol) of 2-Carboxy-2-cyclobutylmethyl-succinic acid 4-ethyl ester to yield 0.501g (60%) of 2-Cyclobutylmethyl-succinic acid 4-ethyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (1H, br s), 4.14 (2H, q), 2.82-2.75 (1H, m), 2.67 (1H, dd), 2.45-2.31 (2H, m), 2.10-2.02 (2H, m), 1.88-1.60 (6H, m), 1.25 (3H, t).

Prepared in a manner similar to that described in Example 24 using 0.425g (1.20mmol) of (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-3-naphthylpropanamide, chloride

(from Compound 96), 0.250g (1.20mmol) of 2-Cyclobutylmethyl-succinic acid 4-ethyl ester, 0.158g (1.20mmol) of HOBt, 0.447g (2.30mmol) of EDC, and 0.42mL (3.5mmol) of NMM to yield 0.534g (85%) of ethyl (3R,S)-3-(N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl}carbamoyl)-4-cyclobutylbutanoate (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 524; $(M+HCO_2^-)^-$ 568.

Prepared in a manner similar to that described in Example 29 using 0.284g (0.54mmol) of ethyl (3R,S)-3-(N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl}carbamoyl)-4-cyclobutylbutanoate (1:1 mixture of diastereoisomers) to yield 0.254g (92%) of 3-(N-hydroxycarbamoyl)(2R,S)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl}-2-(cyclobutylmethyl)propanamide (1:1 mixture of diastereoisomers). The mixture of diastereoisomers was purified by C-18 flash chromatography (MeOH / H_2O) to give 0.015g of 3-(N-hydroxycarbamoyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl}-2-(cyclobutylmethyl)propanamide, $R_f = 0.45$ (solvent: $CHCl_3$ / MeOH / NH_4OH, 90/10/1), MS $(M+H)^+$ 511; $(M-H)^-$ 509; and 0.018g of 3-(N-hydroxycarbamoyl)(2S)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl}-2-(cyclobutylmethyl) propanamide, $R_f = 0.42$ (solvent: $CHCl_3$ / MeOH / NH_4OH, 90/10/1).
MS $(M+H)^+$ 511; $(M-H)^-$ 509.

Example 105: Compound 83:
2-(N-hydroxycarbamoylmethyl)-N-(2-indol-3-ylethyl)-4-methylpentanamide

Prepared in a manner similar to that described in Example 24 using 0.228g (1.10mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.181g (1.10mmol) of tryptamine, 0.152g (1.10mmol) of HOBt, 0.432g (2.30mmol) of EDC, and 0.25mL (2.30mmol) of NMM to yield 0.380g (99%) of ethyl 3-[N-(2-indol-3-ylethyl)carbamoyl]-5-methylhexanoate. MS $(M+H)^+$ 345; $(M+HCO_2^-)^-$ 389.

Prepared in a manner similar to that described in Example 29 using 0.380g (1.10mmol) of ethyl 3-[N-(2-indol-3-ylethyl)carbamoyl]-5-methylhexanoate to yield 0.259g (71%) of 2-(N-hydroxycarbamoylmethyl)-N-(2-indol-3-ylethyl)-4-methylpentanamide.
MS $(M+H)^+$ 332; $(M-H)^-$ 330.

Example 106: Compound 84:
2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[2-(4-phenylphenyl)ethyl]pentanamide

Prepared in a manner similar to that described in Example 24 using 0.228g (1.10mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.222g (1.10mmol) of 2-(4-biphenyl)ethylamine, 0.152g (1.10mmol) of HOBt, 0.432g (2.30mmol) of EDC, and 0.25mL (2.30mmol) of NMM to yield 0.388g (92%) of ethyl 5-methyl-3-{N-[2-(4-phenylphenyl)ethyl]carbamoyl}hexanoate. MS $(M+H)^+$ 382; $(M+HCO_2^-)^-$ 426.

Prepared in a manner similar to that described in Example 29 using 0.188g (0.49mmol) of ethyl 5-methyl-3-{N-[2-(4-phenylphenyl)ethyl]carbamoyl}hexanoate to yield 0.123g (68%) of 2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[2-(4-phenylphenyl)ethyl] pentanamide. MS $(M+H)^+$ 369; $(M-H)^-$ 367.

Example 107: Compound 85:
2-(N-hydroxycarbamoylmethyl)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-indol-3-ylethyl) carbamoyl]-2-indol-3-ylethyl}-4-methylpentanamide

(2S)-N-((1S)-1-carbamoyl-2-indol-3-ylethyl)-2-amino-3-indol-3-ylpropanamide was prepared by stirring (2S)-N-((1S)-1-carbamoyl-2-indol-3-ylethyl)-3-indol-3-yl-2-[(phenyl methoxy) carbonylamino]propanamide (0.84g, 1.6mmol) in Methanol (30mL) along with 10% palladium on carbon (200mg) in hydrogen atmosphere for overnight. The Palladium/carbon was filtered off, the filtrate was rotovaped and dried in vacuum to get the product. Yield: 0.58g (94%).

Ethyl 3-(N-{(1S)-1-[N-((1S)-1-carbamoyl-2-indol-3-ylethyl)carbamoyl]-2-indol-3-ylethyl}carbamoyl)-5-methylhexanoate was prepared from 2-[(ethoxycarbonyl)methyl]-

4-methylpentanoic acid (0.28g, 1.4mmol), (2S)-N-((1S)-1-carbamoyl-2-indol-3-ylethyl)-2-amino-3-indol-3-ylpropanamide (0.58g, 1.5mmol), EDC HCl (0.54g, 2.8mmol), HOBt (0.19g, 1.4mmol), DIEA (487µl, 2.8mmol) and DMF using the procedure from Compound 39. Yield: 0.75g (91%).

2-(N-hydroxycarbamoylmethyl)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-indol-3-ylethyl) carbamoyl]-2-indol-3-ylethyl}-4-methylpentanamide was prepared from Ethyl 3-(N-{(1S)-1-[N-((1S)-1-carbamoyl-2-indol-3-ylethyl)carbamoyl]-2-indol-3-ylethyl} carbamoyl)-5-methylhexanoate (0.29g, 0.5mmol) using the procedure from Compound 88. Yield: 20mg (7%). MS: ($M-H^+$) 559.

Example 108: Compound 86: 2-(N-hydroxycarbamoylmethyl)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-(4-phenylphenyl)ethyl}-4-methylpentanamide

Following the procedure of Example 3, 3-(4-biphenylyl)-n-(tert-butoxycarbonyl)-l-alanine (1g, 2.9mmol), H-IlE-NH_2 HCl (722mg, 1.5mmol), EDC (1.11g, 2mmol), HOBt (444mg, 1mmol), DIEA (1.73mL, 3.5mmol) and dichloromethane (10mL) to yield 1.05g (80%) of (2S)-N-((1S,2S)-1-carbamoyl-2-methylbutyl)-2-[(tert-butoxy)carbonylamino]-3-(4-phenylphenyl)propanamide as a white solid.

Following the procedure of Example 4, (2S)-N-((1S,2S)-1-carbamoyl-2-methylbutyl)-2-[(tert-butoxy)carbonylamino]-3-(4-phenylphenyl)propanamide (1g, 2.2mmol) to yield 355mg of (2S)-N-((1S,2S)-1-carbamoyl-2-methylbutyl)-2-amino-3-(4-phenylphenyl) propanamide as a white solid.

Following the procedure of Example 3, (2S)-N-((1S,2S)-1-carbamoyl-2-methylbutyl)-2-amino-3-(4-phenylphenyl)propanamide (307mg, 0.87mmol), 2-[(ethoxycarbonyl) methyl]-4-methylpentanoic acid (176mg, 0.87mmol), EDC (334mg, 1.74mmol), HOBt (133mg, 0.87mmol), DIEA (0.374mL, 1.74mmol) and dichloromethane (10mL) to yield

315mg (67%) of ethyl 3-(N-{(1S)-1-[N-((1S,2S)-1-carbamoyl-2-methylbutyl) carbamoyl]-2-(4-phenylphenyl)ethyl}carbamoyl)-5-methylhexanoate as a yellow solid.

Using the procedure of Example 2, ethyl 3-(N-{(1S)-1-[N-((1S,2S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-(4-phenylphenyl)ethyl}carbamoyl)-5-methylhexanoate (153mg, 0.28mmol). The crude product was purified by silica gel chromatography (water/methanol, 30:70) to the isolation of 2-(N-hydroxycarbamoylmethyl)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-(4-phenylphenyl)ethyl}-4-methylpentanamide (5mg) in 3% yield, $R_f = 0.53$ (methanol/ ethyl acetate, 1:4). MS $(M+H)^+525$.

Example 109: Compound 88:
2-(N-hydroxycarbamoylmethyl)-N-{(1S)[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide

Prepared in a manner similar to that described in Example 7 using 1.100g (2.40mmol) of 2-[(fluoren-9-ylmethoxy)carbonylamino]-2-(4-phenylphenyl)acetic acid, 0.319g (2.40mmol) of (2S)-2-amino-4-methylpentanamide, 0.331g (2.40mmol) of HOBt, 0.938g (4.90mmol) of EDC, and 0.54mL (4.90mmol) of NMM to yield 1.300g (96%) of (2S,R)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(fluoren-9-ylmethoxy)carbonylamino]-2-(4-phenylphenyl)acetamide (1:1 mixture of diastereoisomers).

To a solution of (2S,R)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(fluoren-9-ylmethoxy) carbonylamino]-2-(4-phenylphenyl)acetamide (1:1 mixture of diastereoisomers) (1.30g, 2.30mmol) in 15mL of DMF was added 1-octanethiol (0.48mL, 2.78mmol) , follow by 1M solution of tetrabutylammonium fluoride in THF (3.50mL, 3.47mmol) at room temperature. The reaction mixture stirred at room temperature for 1 hour. The reaction mixture was concentrated under vacuum. The residue was purified by flash chromatography (ethyl acetate / hexanes / methanol, 2/1/0 to 10/0/1) to give 0.250g (32%) of (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-2-(4-phenylphenyl) acetamide, $R_f = 0.63$ (solvent: MeOH / ethyl acetate, 2/3), 0.204g (26%) of (2R)-N-((1S)-

1-carbamoyl-3-methylbutyl)-2-amino-2-(4-phenylphenyl)acetamide, $R_f = 0.38$ (solvent: MeOH / ethyl acetate, 2/3), and 0.253g (32%) of mixture of two diastereoisomers.

Prepared in a manner similar to that described in Example 7 using 0.130g (0.38mmol) of (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-2-(4-phenylphenyl)acetamide, 0.077g (0.38mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.052g (0.38mmol) of HOBt, 0.147g (0.77mmol) of EDC, and 0.084mL (0.77mmol) of NMM to yield 0.196g (99%) of ethyl (3R,S)-3-(N-{(1S)[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl](4-phenylphenyl)methyl}carbamoyl)-5-methylhexanoate (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 524.

To a solution of NH_2OH-HCl (0.094g, 1.30mmol) in 0.17mL of H_2O was added 5.33M solution of KOH in H_2O (0.51mL, 2.70mmol) and stirred for 10 min. at 0°C. This solution was added to a stirred solution, cooled to 0-5°C, of ethyl (3R,S)-3-(N-{(1S)[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl](4-phenylphenyl)methyl}carbamoyl)-5-methylhexanoate (1:1 mixture of diastereoisomers) (0.196g, 0.37mmol) in 3mL of THF and the reaction emulsion was stirred at 0°C for overnight. After acidification of the reaction solution at 0°C to pH = 5 with 1N HCl, the reaction mixture was concentrated under vacuum. The residue was purified by C-18 flash chromatography (H_2O / methanol) to give 0.705g (37%) of 2-(N-hydroxycarbamoylmethyl)(2R,S)-N-{(1S)[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide (2:3 mixture of diastereoisomers). MS $(M+H)^+$ 511; $(M-H)^-$ 509.

Example 110: Compound 89: 2-(N-hydroxycarbamoylmethyl)-N-[2-benzo[b]thiophen-3-yl-1-(N-methylcarbamoyl)ethyl]-4-methylpentanamide

Prepared in a manner similar to that described in Example 24 using 0.663g (2.07mmol) of (2R)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]propanoic acid, 0.280g (4.1mmol) of methylamine hydrochloride, 0.280g (2.07mmol) of HOBt, 0.780g (4.1mmol) of EDC, and 0.90mL (8.2mmol) of NMM to yield 0.618g (90%) of (2S)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]-N-methylpropanamide.

Prepared in a manner similar to that described in Example 4 using 1.200g (3.59mmol) of (2S)-3-benzo[b]thiophen-3-yl-2-[(tert-butoxy)carbonylamino]-N-methylpropanamide, and 15mL of 4M solution of HCl in 1,4-dioxane to yield 0.716g (85%) of (2S)-2-amino-3-benzo[b]thiophen-3-yl-N-methylpropanamide, hydrochloride.

Prepared in a manner similar to that described in Example 24 using 0.250g (1.07mmol) of (2S)-2-amino-3-benzo[b]thiophen-3-yl-N-methylpropanamide, hydrochloride, 0.215g (1.07mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.150g (1.07mmol) of HOBt, 0.405g (2.14mmol) of EDC, and 0.50mL (4.5mmol) of NMM to yield 0.356g (80%) of ethyl (3R,S)-3-{N-[(1R)-2-benzo[b]thiophen-3-yl-1-(N-methylcarbamoyl) ethyl]carbamoyl}-5-methylhexanoate (1:1 mixture of diastereoisomers).

Prepared in a manner similar to that described in Compound 88 using 0.356g (0.85mmol) of ethyl (3R,S)-3-{N-[(1R)-2-benzo[b]thiophen-3-yl-1-(N-methylcarbamoyl)ethyl] carbamoyl}-5-methylhexanoate (1:1 mixture of diastereoisomers) to yield 0.030g (9%) of 2-(N-hydroxycarbamoylmethyl)(2R,S)-N-[(1R)-2-benzo[b]thiophen-3-yl-1-(N-methylcarbamoyl)ethyl]-4-methylpentanamide (1:1 mixture of diastereoisomers).
MS $(M+H)^+$ 406; $(M-H)^-$ 404.

Example 111: Compound 90: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S,2S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-naphthylethyl}hexanamide

Following the procedure of Example 3, (2S)-N-((1S)-1-carbamoyl-2-methylbutyl)-2-amino-3-naphthylpropanamide (209mg, 0.64mmol), (2R)-2-({N-[(2,4-dimethoxyphenyl) methyl]-N-[(4-methoxyphenyl)methoxy]carbamoyl}methyl)hexanoic acid (355mg, 0.77mmol), EDC (246mg, 1.28mmol), HOBt (98mg, 0.64mmol), DIEA (0.223mL, 1.28mmol) and dichloromethane (10mL) to yield 338mg (69%) of (2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-naphthylethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide as an off white solid.

Following the procedure of Example 15, (2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-naphthylethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-butyl-N'-[(4-methoxyphenyl)methoxy]butane-1,4-diamide (100mg, 0.13mmol) and 4/1 (v/v) mixture of trifluoroacetic acid and trimethylsilyl bromide. The crude product was washed with methanol to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S,2S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-naphthylethyl}hexanamide (4mg) in 6% yield, $R_f = 0.31$ (methanol/ethyl acetate, 1:4). MS $(M+H)^+$499.

Example 112: Compound 91:
N-{2-(N-hydroxycarbamoyl)(1R)-1-[(2,3,4,5,6-pentafluorophenyl)methyl]ethyl}(2R)-2-[(tert-butoxy)carbonylamino]-3-(2-naphthyl)propanamide

(3R)-3-[(tert-butoxy)carbonylamino]-4-(2,3,4,5,6-pentafluorophenyl)-N-(phenyl methoxy) butanamide was prepared from boc-(r)-3-amino-4-pentafluorophenyl butanoic acid (1.01g, 2.75mmol), O-benzylhydroxylamine (0.68g, 5.5mmol), EDC HCl (1.06g, 5.5mmol), HOBt (0.42g, 5.5mmol), DIEA (0.96mL, 5.5mmol) and DMF (15mL) using the procedure of Compound 39. Yield: 1.1g (84%).

(3R)-3-amino-4-(2,3,4,5,6-pentafluorophenyl)-N-(phenylmethoxy)butanamide was prepared from (3R)-3-[(tert-butoxy)carbonylamino]-4-(2,3,4,5,6-pentafluorophenyl)-N-(phenylmethoxy)butanamide (0.71g, 1.5mmol) and 4N HCl/dioxane (10mL) using the procedure from Example 4. Yield: 0.25g (45%).

(3R)-3-{(2R)-2-[(tert-butoxy)carbonylamino]-3-(2-naphthyl)propanoylamino}-4-(2,3,4,5,6-pentafluorophenyl)-N-(phenylmethoxy)butanamide was prepared from boc-D-2-naphthylalanine (315mg, 1mmol), (3R)-3-amino-4-(2,3,4,5,6-pentafluorophenyl)-N-(phenylmethoxy)butanamide (225mg, 0.6mmol), EDC HCl (384mg, 2mmol), HOBt (135mg, 1mmol), DIEA (348µl 2mmol), dichloromethane (10mL) using the procedure from Example 3. Yield: 360mg (54%).

N-{2-(N-hydroxycarbamoyl)(1R)-1-[(2,3,4,5,6-pentafluorophenyl)methyl]ethyl}(2R)-2-[(tert-butoxy)carbonylamino]-3-(2-naphthyl)propanamide was prepared by stirring the solution of (3R)-3-{(2R)-2-[(tert-butoxy)carbonylamino]-3-(2-naphthyl) propanoyl amino}-4-(2,3,4,5,6-pentafluorophenyl)-N-(phenylmethoxy)butanamide (200mg, 0.3mmol), in methanol, in presence of 10% palladium/carbon in hydrogen atmosphere overnight. The palladium/carbon was filtered off. The filtrate on evaporation gave a solid. Yield: 85mg (64%). MS: ($M+H^+$- boc group) 482.

Example 113: Compound 92: 2-(N-hydroxycarbamoylmethyl)-N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl]ethyl}octanamide

Prepared in a manner similar to that described in Example 23 using 1.00g (3.31mmol) of tert-butyl ethyl 2-[(tert-butyl)oxycarbonyl]butane-1,4-dioate, 1.40g (6.60mmol) of iodohexane, 0.132g (3.31mmol) of NaH to yield 1.22g (95%) of tert-butyl ethyl 2-[(tert-butyl)oxycarbonyl]-2-hexylbutane-1,4-dioate.

Prepared in a manner similar to that described in Example 23 using 1.22g (3.160mmol) of tert-butyl ethyl 2-[(tert-butyl)oxycarbonyl]-2-hexylbutane-1,4-dioate, and 10mL of TFA to yield 0.823g (95%) of 2-[(ethoxycarbonyl)methyl]-2-hexylpropanedioic acid.
Prepared in a manner similar to that described in Example 23 using 0.823g (3.00mmol) of 2-[(ethoxycarbonyl)methyl]-2-hexylpropanedioic acid to yield 0.590g (86%) of 2-[(ethoxycarbonyl)methyl]octanoic acid.

Prepared in a manner similar to that described in Example 24 using 0.250g (0.74mmol) of (2S)-2-amino-3-(2-naphthyl)-N-benzylpropanamide, hydrochloride (from Compound 100), 0.170g (0.74mmol) of 2-[(ethoxycarbonyl)methyl]octanoic acid, 0.100g (0.74mmol) of HOBt, 0.280g (1.47mmol) of EDC, and 0.24mL (2.19mmol) of NMM to yield 0.225g (59%) of ethyl (3R,S)-3-(N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl] ethyl}carbamoyl)nonanoate (1:1 mixture of diastereoisomers).

Prepared in a manner similar to that described in Compound 88 using 0.225g (0.43mmol) of ethyl (3R,S)-3-(N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl]ethyl}carbamoyl) nonanoate (1:1 mixture of diastereoisomers) to yield 0.030g (14%) of 2-(N-hydroxycarbamoylmethyl)(2R,S)-N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl]ethyl} octanamide (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 504; $(M-H)^-$ 502.

Example 114: Compound 93: 2-(N-hydroxycarbamoylmethyl)-N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl]ethyl}heptanamide

Prepared in a manner similar to that described in Example 23 using 2.00g (6.62mmol) of tert-butyl ethyl 2-[(tert-butyl)oxycarbonyl]butane-1,4-dioate, 2.62g (13.23mmol) of iodopentane, 0.265g (6.62mmol) of NaH to yield 2.02g (82%) of tert-butyl ethyl 2-[(tert-butyl)oxycarbonyl]-2-pentylbutane-1,4-dioate.

Prepared in a manner similar to that described in Example 23 using 2.02g (5.43mmol) of tert-butyl ethyl 2-[(tert-butyl)oxycarbonyl]-2-pentylbutane-1,4-dioate, and 15mL of TFA to yield 1.383g (98%) of 2-[(ethoxycarbonyl)methyl]-2-pentylpropanedioic acid.

Prepared in a manner similar to that described in Example 23 using 1.383g (5.32mmol) of 2-[(ethoxycarbonyl)methyl]-2-pentylpropanedioic acid to yield 1.11g (97%) of 2-[(ethoxycarbonyl)methyl]heptanoic acid.

Prepared in a manner similar to that described in Example 24 using 0.250g (0.74mmol) of (2S)-2-amino-3-(2-naphthyl)-N-benzylpropanamide, hydrochloride (from Compound 100), 0.160g (0.74mmol) of 2-[(ethoxycarbonyl)methyl]heptanoic acid, 0.100g (0.74mmol) of HOBt, 0.280g (1.47mmol) of EDC, and 0.24mL (2.19mmol) of NMM to yield 0.230g (62%) of ethyl (3R,S)-3-(N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl] ethyl}carbamoyl)octanoate (1:1 mixture of diastereoisomers).

Prepared in a manner similar to that described in Compound 88 using 0.230g (0.46mmol) of ethyl (3R,S)-3-(N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl]ethyl}carbamoyl)

octanoate (1:1 mixture of diastereoisomers) to yield 0.032g (14%) of 2-(N-hydroxycarbamoylmethyl)(2R,S)-N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl] ethyl}heptanamide (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 490; $(M-H)^-$ 488.

Example 115: Compound 94: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoylethyl)carbamoyl]-2-naphthylethyl}-4-methylpentanamide

Following the procedure of Example 3, (2S)-2-amino-N-(carbamoylethyl)-3-naphthylpropanamide (120mg, 0.42mmol), (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-(phenylmethoxy)carbamoyl}methyl)-4-methylpentanoic acid, sodium salt (243mg, 0.5mmol), EDC (192mg, 1mmol), HOBt (77mg, 0.5mmol), DIEA (0.087mL, 0.5mmol) and dichloromethane (15mL) to yield 331mg (95%) of (2R)-N-{(1S)-1-[N-(carbamoylethyl)carbamoyl]-2-naphthylethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide as a white solid.

(2R)-N-{(1S)-1-[N-(carbamoylethyl)carbamoyl]-2-naphthylethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide (141mg, 0.2mmol) and 4/1 (v/v) mixture of trifluoroacetic acid and trimethylsilyl bromide were stirred under nitrogen for five minutes. The reaction was complete by LC after 3 hours. Added methanol and concentrated. The crude residue was treated with ether to give a precipitate to yield 90mg (82%) of (2R)-N-{(1S)-1-[N-(carbamoylethyl) carbamoyl]-2-naphthylethyl}-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide as a white solid.

Following the procedure of Example 91, (2R)-N-{(1S)-1-[N-(carbamoylethyl)carbamoyl] -2-naphthylethyl}-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide (80mg, 0.15mmol). The crude product was purified by silica gel chromatography (water/methanol, 40:60) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoylethyl)carbamoyl]-2-naphthylethyl}-4-methylpentanamide (9mg) in 13% yield, $R_f = 0.4$ (methanol/ ethyl acetate, 1:4). MS $(M+H)^-$455.

Example 116: Compound 95: 2-(N-hydroxycarbamoylmethyl)-N-{(1S)-2-(2-naphthyl)-1-[N-(2-phenylethyl)carbamoyl]ethyl}-4-methylpentanamide

Prepared in a manner similar to that described in Example 24 using 1.00g (3.17mmol) of (S)-(-)-2-(tert-butoxycarbonylamino)-3-(2-naphthyl)propanoic acid, 0.40mL (3.17mmol) of phenethylamine, 0.428g (3.17mmol) of HOBt, 1.216g (6.34mmol) of EDC, and 0.697mL (6.34mmol) of NMM to yield 1.290g (96%) of (S)-(2-Naphthalen-2-yl-1-phenethylcarbamoyl-ethyl)-carbamic acid tert-butyl ester.
MS $(M+H)^+$ 419; $(M+HCO_2^-)^-$ 463.

Prepared in a manner similar to that described in Example 4 using 1.200g (2.87mmol) of (S)-(2-Naphthalen-2-yl-1-phenethylcarbamoyl-ethyl)-carbamic acid tert-butyl ester, and 15mL of 4M solution of HCl in 1,4-dioxane to yield 0.966g (95%) of (2S)-2-amino-3-(2-naphthyl)-N-(2-phenylethyl)propanamide, hydrochloride.

Prepared in a manner similar to that described in Example 24 using 0.246g (0.69mmol) of (2S)-2-amino-3-(2-naphthyl)-N-(2-phenylethyl)propanamide, hydrochloride, 0.140g (0.69mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.094g (0.69mmol) of HOBt, 0.266g (1.39mmol) of EDC, and 0.23mL (2.09mmol) of NMM to yield 0.242g (70%) of ethyl (3R,S)-3-(N-{(1S)-2-(2-naphthyl)-1-[N-(2-phenylethyl)carbamoyl]ethyl} carbamoyl)-5-methylhexanoate (1:1 mixture of diastereoisomers).
MS $(M+H)^+$ 503; $(M+HCO_2^-)^-$ 547.

Prepared in a manner similar to that described in Compound 88 using 0.242g (0.48mmol) of ethyl (3R,S)-3-(N-{(1S)-2-(2-naphthyl)-1-[N-(2-phenylethyl)carbamoyl]ethyl} carbamoyl)-5-methylhexanoate (1:1 mixture of diastereoisomers) to yield 0.110g (47%) of 2-(N-hydroxycarbamoylmethyl)(2R,S)-N-{(1S)-2-(2-naphthyl)-1-[N-(2-phenylethyl) carbamoyl]ethyl}-4-methylpentanamide (1:1 mixture of diastereoisomers).
MS $(M+H)^+$ 490; $(M-H)^-$ 488.

Example 117: Compounds 96 and 138: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl}-4-

methylpentanamide and 2-(N-hydroxycarbamoylmethyl)(2S)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-2-naphthylethyl}-4-methylpentanamide

(2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(tert-butoxy)carbonylamino]-3-naphthyl propanamide was prepared from (2S)-2-[(tert-butoxy)carbonylamino]-3-naphthyl propanoic acid (0.63g, 2mmol), (2S)-2-amino-4-methylpentanamide (0.26g, 2mmol), EDC HCl (0.77g, 4mmol), HOBt (0.27g, 2mmol), DIEA (0.35mL, 2mmol) and DMF (16mL) using the procedure in Compound 39. Yield: 0.75g (88%).

(2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-3-naphthylpropanamide, was prepared from (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(tert-butoxy) carbonyl amino] -3-naphthyl propanamide (0.43g, 1mmol) and 4N HCl/dioxane (10mL) using the procedure from Example 4. Yield: 0.34g (92%).

ethyl 3-(N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl} carbamoyl)-5-methylhexanoate was prepared from 2-[(ethoxycarbonyl)methyl]-4-methyl pentanoic acid (0.20g, 1mmol), (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-amino-3-naphthylpropanamide, (0.22g, 0.6mmol), EDC HCl (0.38g, 2mmol), HOBt (0.135g, 1mmol), DIEA (0.35mL, 2mmol) and dichloromethane (10mL) using the procedure from Example 3. Yield: 028g (91%).

2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-2-naphthylethyl}-4-methylpentanamide (Compound 96) and 2-(N-hydroxycarbamoylmethyl)(2S)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-2-naphthylethyl}-4-methylpentanamide (Compound 138).

The title compounds were prepared from ethyl 3-(N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl} carbamoyl)-5-methylhexanoate (0.16g, 0.3mmol) using the procedure from Compound 88. The two isomers were separated using C-18 reverse phase silica gel using the mixtures of methanol and water as eluents.

2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-2-naphthylethyl}-4-methylpentanamide (Compound 96) has Rf = 1.875' in HPLC column. MS: ($M+H^+$) 499.

^1H NMR: (300 MHz,DMSO-d_6): 10.41 δ (1H bs); 8.71 δ (1H bs); 8.33 δ (1H d); 8.26 δ (1H d); 8.20 δ (2H dm); 7.93 δ (1H m) 7.78 δ (2H m); 7.38 δ (2H m); 7.10 δ (1H m); 7.00 δ (1H m) 4.61 δ (1H m) 4.26 δ (1H m); 3.63 δ (1H m); 3.40 δ (1H m); 3.24 δ (2H m) 2.64 δ (1H m); 1.90 δ (1H m); 1.43 δ (4H m); 0.94 δ (6H m). 0.75 δ (3H dm); 0.73 δ (3H m).

2-(N-hydroxycarbamoylmethyl)(2S)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-2-naphthylethyl}-4-methylpentanamide (Compound 138) has Rf = 2.158' in HPLC column. MS: ($M+H^+$) 499.

^1H NMR: (300 MHz, DMSO-d_6): 10.56 δ (1H bs); 8.79 δ (1H bs); 8.67 δ (1H d); 8.21 δ (1H d); 8.13 δ (1H dm); 7.93 δ (1H d) 7.78 δ (1H m); 7.54 δ (3H m); 7.38 δ (1H m); 7.09 δ (1H m) 7.01 δ (1H d); 4.46 δ (1H m) 4.41 δ (1H m); 3.85 δ (1H m); 3.30 δ (1H m); 3.04 δ (1H m) 2.59 δ (1H m); 2.15 δ (1H m); 1.99 δ (1H m); 1.86 δ (1H m); 1.68 δ (1H m); 1.56 δ (1H m); 1.06 δ (1H m); 0.92 δ (7H m); 0.75 δ (6H m).

Example 118: Compound 98: 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)-1-[N-((1S)-1-carbamoylethyl)carbamoyl]-2-(2-naphthyl)ethyl}-4-methylpentanamide

Following the procedure of Example 4, (2R)-N-((1S)-1-carbamoylethyl)-2-[(tert-butoxy) carbonylamino]-3-(2-naphthyl)propanamide (1.4g, 3.6mmol) to yield 576mg (56%) of (2R)-N-((1S)-1-carbamoylethyl)-2-amino-3-(2-naphthyl)propanamide as a white solid.

Following the procedure of Example 3, (2R)-N-((1S)-1-carbamoylethyl)-2-amino-3-(2-naphthyl)propanamide (143mg, 0.5mmol), (2R)-2-({N-[(2,4-dimethoxyphenyl)methyl]-N-(phenylmethoxy)carbamoyl}methyl)-4-methylpentanoic acid, sodium salt (243mg, 0.5mmol), EDC (192mg, 1mmol), HOBt (77mg, 0.5mmol), DIEA (0.087mL, 0.5mmol)

and dichloromethane (15mL) to yield 220mg (63%) of (2R)-N-{(1R)-1-[N-((1S)-1-carbamoylethyl)carbamoyl]-2-(2-naphthyl)ethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide as a white solid.

(2R)-N-{(1R)-1-[N-((1S)-1-carbamoylethyl)carbamoyl]-2-(2-naphthyl)ethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide (100mg, 0.14mmol) and 4/1 (v/v) mixture of trifluoroacetic acid and trimethylsilyl bromide were stirred under nitrogen for five minutes. The reaction was complete by LC after 3 hours. Added methanol and concentrated. The crude residue was treated with ether to give a precipitate to yield 99mg of (2R)-N-{(1R)-1-[N-((1S)-1-carbamoylethyl) carbamoyl]-2-(2-naphthyl)ethyl}-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide as a pink solid.

Following the procedure of Example 91, (2R)-N-{(1R)-1-[N-((1S)-1-carbamoylethyl) carbamoyl]-2-(2-naphthyl)ethyl}-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide (86mg, 0.15mmol). The crude product was purified by silica gel chromatography (water/methanol, 30:70) to the isolation of 2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)-1-[N-((1S)-1-carbamoylethyl)carbamoyl]-2-(2-naphthyl)ethyl}-4-methylpentanamide (12mg) in 13% yield, $R_f = 0.16$ (methanol/ chloroform, 5:95). MS $(M+H)^+$457.

Example 119: Compound 99: 2-(N-hydroxycarbamoylmethyl)-N-[(1S)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl]-4-methylpentanamide

Prepared in a manner similar to that described in Example 24 using 3.00g (9.52mmol) of (S)-(-)-2-(tert-butoxycarbonylamino)-3-(2-naphthyl)propanoic acid, 1.28g (19.10mmol) of methylamine hydrochloride, 1.29g (9.52mmol) of HOBt, 3.61g (19.00mmol) of EDC, and 4.2mL (38.26mmol) of NMM to yield 2.81g (90%) of (2S)-2-[(tert-butoxy) carbonylamino]-N-methyl-3-(2-naphthyl)propanamide.

Prepared in a manner similar to that described in Example 4 using 2.81g (8.57mmol) of (2S)-2-[(tert-butoxy)carbonylamino]-N-methyl-3-(2-naphthyl)propanamide, and 15mL of 4M solution of HCl in 1,4-dioxane to yield 1.50g (66%) of (2S)-2-amino-N-methyl-3-(2-naphthyl)propanamide, hydrochloride.

Prepared in a manner similar to that described in Example 24 using 0.200g (0.75mmol) of (2S)-2-amino-N-methyl-3-(2-naphthyl)propanamide, hydrochloride, 0.152g (0.75mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.103g (0.75mmol) of HOBt, 0.300g (1.50mmol) of EDC, and 0.32mL (2.80mmol) of NMM to yield 0.250g (81%) of ethyl (3R,S)-3-{N-[(1S)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl]carbamoyl}-5-methylhexanoate (1:1 mixture of diastereoisomers).

Prepared in a manner similar to that described in Compound 88 using 0.250g (0.61mmol) of ethyl (3R,S)-3-{N-[(1R)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl]carbamoyl}-5-methylhexanoate (1:1 mixture of diastereoisomers) to yield 0.029g (12%) of 2-(N-hydroxycarbamoylmethyl)(2R,S)-N-[(1S)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl]-4-methylpentanamide (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 400; $(M-H)^-$ 398.

Example 120: Compound 100: 2-(N-hydroxycarbamoylmethyl)-N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl]ethyl}-4-methylpentanamide

Prepared in a manner similar to that described in Example 24 using 1.00g (3.17mmol) of (S)-(-)-2-(tert-butoxycarbonylamino)-3-(2-naphthyl)propanoic acid, 0.35mL (3.17mmol) of benzylamine, 0.428g (3.17mmol) of HOBt, 1.216g (6.34mmol) of EDC, and 0.697mL (6.34mmol) of NMM to yield 1.192g (92%) of (2S)-2-[(tert-butoxy)carbonylamino]-3-(2-naphthyl)-N-benzylpropanamide. MS $(M+H)^+$ 405; $(M+HCO_2^-)^-$ 449.

Prepared in a manner similar to that described in Example 4 using 1.100g (2.72mmol) of (2S)-2-[(tert-butoxy)carbonylamino]-3-(2-naphthyl)-N-benzylpropanamide, and 15mL of 4M solution of HCl in 1,4-dioxane to yield 0.920g (99%) of (2S)-2-amino-3-(2-naphthyl)-N-benzylpropanamide, hydrochloride.

Prepared in a manner similar to that described in Example 24 using 0.219g (0.64mmol) of (2S)-2-amino-3-(2-naphthyl)-N-benzylpropanamide, hydrochloride, 0.130g (0.64mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.087g (0.64mmol) of HOBt, 0.247g (1.30mmol) of EDC, and 0.21mL (1.90mmol) of NMM to yield 0.246g (79%) of ethyl (3R,S)-3-(N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl]ethyl}carbamoyl)-5-methylhexanoate (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 489; $(M+HCO_2^-)^-$ 533.

Prepared in a manner similar to that described in Compound 88 using 0.246g (0.50mmol) of ethyl (3R)-3-(N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl]ethyl}carbamoyl)-5-methylhexanoate (1:1 mixture of diastereoisomers) to yield 0.021g (9%) of 2-(N-hydroxycarbamoylmethyl)(2R,S)-N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl]ethyl}-4-methylpentanamide (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 476; $(M-H)^-$ 474.

Example 121: Compound 101: 2-(N-hydroxycarbamoylmethyl)-N-[(1S,2R)-1-(N-methylcarbamoyl)-2-(phenylmethoxy)propyl]-4-methylpentanamide

Prepared in a manner similar to that described in Example 24 using 2g (6.5mmol) of Boc-l-thr(bzl)-OH, 0.87g (13mmol) of methylamine hydrochloride, 0.873g (6.5mmol) of HOBt, 2.46g (13mmol) of EDC, and 2.8mL (26mmol) of NMM to yield (2S,3R)-2-[(tert-butoxy)carbonylamino]-N-methyl-3-(phenylmethoxy)butanamide. Without futher purification the product was used in the next reaction

Prepared in a manner similar to that described in Example 4 using of (2S,3R)-2-[(tert-butoxy)carbonylamino]-N-methyl-3-(phenylmethoxy)butanamide, and 15mL of 4M solution of HCl in 1,4-dioxane to yield 1.5g (88%) of (2S,3R)-2-amino-N-methyl-3-(phenylmethoxy)butanamide, chloride.

Prepared in a manner similar to that described in Example 24 using 0.100g (0.38mmol) of 2S,3R)-2-amino-N-methyl-3-(phenylmethoxy)butanamide, chloride, 0.15g (0.74mmol) of 2-[(ethoxycarbonyl)methyl]-4-methylpentanoic acid, 0.050g (0.37mmol) of HOBt,

0.150g (0.79mmol) of EDC, and 0.2mL (1.5mmol) of NMM to yield 0.125g (81%) of ethyl 3-{N-[(1S,2R)-1-(N-methylcarbamoyl)-2-(phenylmethoxy)propyl]carbamoyl}-5-methylhexanoate.

Prepared in a manner similar to that described in Example 34 using 0.100g (0.25mmol) ethyl 3-{N-[(1S,2R)-1-(N-methylcarbamoyl)-2-(phenylmethoxy)propyl]carbamoyl}-5-methylhexanoate to yield 0.035g (37%) of 3-{N-[(1S,2R)-1-(N-methylcarbamoyl)-2-(phenylmethoxy)propyl]carbamoyl}-5-methylhexanoic acid.

Prepared in a manner similar to that described in Example 24 using 0.035g (0.09mmol) of 3-{N-[(1S,2R)-1-(N-methylcarbamoyl)-2-(phenylmethoxy)propyl]carbamoyl}-5-methylhexanoic acid, 0.015g (0.09mmol) of o-benzylhydroxylamine hydrochloride, 0.012g (0.08mmol) of HOBt, 0.035g (0.18mmol) of EDC, and 0.02mL (0.18mmol) of NMM to yield 0.040g (92%) of N-[(1S,2R)-1-(N-methylcarbamoyl)-2-(phenylmethoxy) propyl]-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide.

Prepared in a manner similar to that described in Example 21 using 0.040g (0.082mmol) of N-[(1S,2R)-1-(N-methylcarbamoyl)-2-(phenylmethoxy)propyl]-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide and palladium on charcoal (0.01g) to give 0.03g (93%) of 2-(N-hydroxycarbamoylmethyl)-N-[(1S,2R)-1-(N-methylcarbamoyl)-2-(phenylmethoxy)propyl]-4-methylpentanamide (1:1 mixture of diastereoisomers). MS $(M+H)^+$ 394; $(M-H)^-$ 392.

Example 122: Compound 102:
2-(N-hydroxycarbamoylmethyl)-N-(2-indol-3-ylethyl)-4-phenylbutanamide

Prepared in a manner similar to that described in Example 23 using 4.00g (13.20mmol) of tert-butyl ethyl 2-[(tert-butyl)oxycarbonyl]butane-1,4-dioate, 1.92mL (13.20mmol) of (2-iodoethyl)benzene, 0.592g (13.20mmol) of NaH to yield 4.564g (85%) of tert-butyl ethyl 2-[(tert-butyl)oxycarbonyl]-2-(2-phenylethyl)butane-1,4-dioate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.15 (5H, m), 4.13 (2H, q), 2.96 (2H, s), 2.59-2.53 (2H, m), 2.23-2.17 (2H, m), 1.48 (18H, s), 1.25 (3H, t).

Prepared in a manner similar to that described in Example 23 using 2.00g (4.90mmol) of tert-butyl ethyl 2-[(tert-butyl)oxycarbonyl]-2-(2-phenylethyl)butane-1,4-dioate, 0.5mL of Et_3SiH, and 12mL of TFA to yield 1.419g (98%) of 2-[(ethoxycarbonyl)methyl]-2-(2-phenylethyl)propanedioic acid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (2H, br s), 7.31-7.13 (5H, m), 4.16 (2H, q), 3.18 (2H, s), 2.68-2.62 (2H, m), 2.27-2.20 (2H, m), 1.26 (3H, t).

Prepared in a manner similar to that described in Example 23 using 1.419g (4.82mmol) of 2-[(ethoxycarbonyl)methyl]-2-(2-phenylethyl)propanedioic acid to yield 1.151g (95%) of 2-[(ethoxycarbonyl)methyl]-4-phenylbutanoic acid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.50 (1H, br s), 7.29-7.17 (5H, m), 4.14 (2H, q), 2.94-2.88 (1H, m), 2.80-2.66 (3H, m), 2.51 (1H, dd), 2.08-2.01 (1H, m), 1.92-1.82 (1H, m), 1.25 (3H, t).

Prepared in a manner similar to that described in Example 24 using 0.104g (0.42mmol) of 2-[(ethoxycarbonyl)methyl]-4-phenylbutanoic acid, 0.067g (0.42mmol) of 2-indol-3-ylethylamine, 0.056g (0.42mmol) of HOBt, 0.159g (0.83mmol) of EDC, and 0.09mL (0.83mmol) of NMM to yield 0.158g (97%) of ethyl 3-[N-(2-indol-3-ylethyl)carbamoyl]-5-phenylpentanoate.

Prepared in a manner similar to that described in Example 26 using 0.158g (0.40mmol) of ethyl 3-[N-(2-indol-3-ylethyl)carbamoyl]-5-phenylpentanoate to yield 0.094g (63%) of 3-[2-(1H-Indol-3-yl)-ethylcarbamoyl]-5-phenyl-pentanoic acid, lithium salt.

Prepared in a manner similar to that described in Example 24 using 0.074g (0.20mmol) of 3-[2-(1H-Indol-3-yl)-ethylcarbamoyl]-5-phenyl-pentanoic acid, lithium salt, 0.032g (0.20mmol) of O-benzylhydroxylamine hydrochloride, 0.027g (0.20mmol) of HOBt, 0.077g (0.4mmol) of EDC, and 0.044mL (0.4mmol) of NMM to yield 0.078g (83%) of N-(2-indol-3-ylethyl)-2-(2-phenylethyl)-N'-(phenylmethoxy)butane-1,4-diamide. MS $(M+H)^+$ 470; $(M-H)^-$ 468.

Prepared in a manner similar to that described in Example 21 using 0.077g (0.16mmol) of N-(2-indol-3-ylethyl)-2-(2-phenylethyl)-N'-(phenylmethoxy)butane-1,4-diamide and 0.023g of 10% of Pd/C to yield 0.053g (88%) of 2-(N-hydroxycarbamoylmethyl)-N-(2-indol-3-ylethyl)-4-phenylbutanamide. MS $(M+H)^+$ 380; $(M-H)^-$ 378.

Example 123: Compound 103: 2-(N-hydroxycarbamoylmethyl)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl) carbamoyl]-2-naphthylethyl}-4-methylpentanamide

(2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(tert-butoxy)carbonylamino]-3-naphthylpropanamide was prepared from (2S)-2-[(tert-butoxy)carbonylamino]-3-naphthylpropanoic acid (0.63g, 2mmol), (2S,3S)-2-amino-3-methylpentanamide, hydrochloride (0.50g, 3mmol), EDC·HCl (0.77g, 4mmol), HOBt (0.23g, 2mmol), DIEA (1.22mL, 7mmol) and dichloromethane (20mL) using the procedure from Example 3. Yield: 0.69g (80%).

(2S)-N-((1S)-1-carbamoyl-2-methylbutyl)-2-amino-3-naphthylpropanamide was prepared from (2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-2-[(tert-butoxy)carbonylamino]-3-naphthylpropanamide (0.60g, 1.4mmol), and 4N HCl/dioxane (10mL) using the procedure as in Example 4. Yield: 0.25g (54%).

N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-naphthylethyl}-N'-[(2,4-dimethoxyphenyl)methyl]-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide was prepared from sodium salt 2-({N-[(2,4-dimethoxyphenyl)methyl]-N-(phenyl methoxy) carbamoyl}methyl)-4-methylpentanoic acid (0.23g, 0.5mmol), (2S)-N-((1S)-1-

carbamoyl-2-methylbutyl)-2-amino-3-naphthylpropanamide (0.17g, 0.5mmol), EDC HCl (192mg, 1.0mmol), HOBt (135mg, 1.0mmol), DIEA (87μL, 0.5mmol), dichloromethane (5mL) using the procedure from Example 3. Yield: 0.30g (81%).

N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-naphthylethyl}-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide was prepared by stirring N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-naphthylethyl}-N'-[(2,4-dimethoxy phenyl)methyl]-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide (0.10g, 0.135mmol) with trifluoro acetic acid /trimethylsilylbromide 4/1 (1.0mL) at room temperature under nitrogen for 3 hours. The solvent was rotovaped, the residue was triturated with ether to obtain a solid. Yield: 75mg (94%).

2-(N-hydroxycarbamoylmethyl)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl) carbamoyl]-2-naphthylethyl}-4-methylpentanamide was prepared by stirring a methanol (10mL) solution of N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-naphthylethyl}-2-(2-methylpropyl)-N'-(phenylmethoxy)butane-1,4-diamide (75mg, 0.13mmol) with 10% palladium/carbon (25mg) in presence of hydrogen. The product was purified by RP C-18 column using methanol and water mixtures as eluents. The product contained mostly the single isomer of (91/9) 2-(N-hydroxycarbamoylmethyl) (2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-naphthylethyl}-4-methylpentanamide. MS: ($M+H^+$) 499.

Example 124: Compound 104: 7-aza-6-oxo-7-(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))heptanoic acid

3-[3-(trifluoromethyl)phenoxy]benzaldehyde (2.5g, 9.4mmol) and thiosemicarbazide (0.85g, 9.4mmol) in 25mL ethanol was placed in microwave at 160°C for 5 mins to give 2.8g (88%) of [((1E)-1-aza-2-{3-[3-(trifluoromethyl)phenoxy]phenyl}vinyl) amino]aminomethane-1-thione

Prepared in a manner similar to that described in Example 32 using 2.8g (8.25mmol) of [((1E)-1-aza-2-{3-[3-(trifluoromethyl)phenoxy]phenyl}vinyl)amino]aminomethane-1-thione to yield 2.7g (99%) of 5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazole-2-ylamine.

5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazole-2-ylamine (2.7g, 8mmol) and trifluoroacetic anhydride (1.8mL, 8mmol) were stirred in 20mL dichloromethane at room temperature for overnight to yield 3.3g (95%) of 2,2,2-trifluoro-N-(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazol-2-yl))acetamide.

Prepared in a manner similar to that described in Example 33 using 2.79g (6.44mmol) of 2,2,2-trifluoro-N-(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazol-2-yl))acetamide to yield 1.25g (36%) of 1-aza-3,3,3-trifluoro-1-(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))acetone.

1-aza-3,3,3-trifluoro-1-(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy] phenyl} (1,3,4-thiadiazolin-2-ylidene))acetone (1.25g 2.32mmol) and potassium carbonate (0.4g, 2.32mmol) were stirred in methanol (20mL) for overnight to yield 0.85g (83%) of 3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazolin-2-imine.

3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazolin-2-imine (0.2g, 0.45mmol), 5-(chloroformyl)valeric acid methyl ester (0.16g, 0.89mmol), DMAP (0.11g, 0.9mmol) in 20mL dichloromethane were stirred at room temperature for 2 hours. The crude residue was washed with brine and extracted with dichloromethane. Dichloromethane was dried over sodium sulfate, filtered, and concentrated to yield 0.2g (76%) of methyl 7-aza-6-oxo-7-(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl) phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))heptanoate.

Prepared in a manner similar to that described in Example 34 using 0.200g (0.34mmol) methyl 7-aza-6-oxo-7-(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}

(1,3,4-thiadiazolin-2-ylidene))heptanoate to yield 0.18g (90%) of 5-{3-Phenethyl-5-[3-(3-trifluoromethyl-phenoxy)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidenecarbamoyl}-pentanoic acid as a yellow solid. MS $(M+H)^+$ 570; $(M-H)^-$ 568.

Example 125: Compound 105: Mixture of 2-[(2-(N-hydroxycarbamoyl) (1S,2S)cyclohexyl)carbonylamino](2S)-N-((1S)-1-carbamoylpropyl)-3-naphthylpropanamide and 2-[(2-(N-hydroxycarbamoyl) (1R,2R)cyclohexyl) carbonylamino](2S)-N-((1S)-1-carbamoylpropyl)-3-naphthyl propanamide

(2S)-N-((1S)-1-carbamoylpropyl)-2-[(tert-butoxy)carbonylamino]-3-naphthylpropan amide was prepared from (2S)-2-[(tert-butoxy)carbonylamino]-3-naphthylpropanoic acid (0.63g, 2mmol), (2S)-2-aminobutanamide (0.20g, 2mmol), EDC HCl (0.58g, 3mmol), HOBt (0.31g, 2mmol), DIEA (0.52mL, 3mmol), and 20mL using the procedure from Compound 39. Yield: 0.64g (79%).

(2S)-N-((1S)-1-carbamoylpropyl)-2-amino-3-naphthylpropanamide was prepared by stirring (2S)-N-((1S)-1-carbamoylpropyl)-2-[(tert-butoxy)carbonylamino]-3-naphthylpropan amide (0.80g, 2mmol) in 4N HCl/dioxane (10mL) using the procedure from Example 4. Yield: 0.30g (50%).

Mixture of (1R,2R)-2-(N-{(1S)-1-[N-((1S)-1-carbamoylpropyl)carbamoyl]-2-naphthylethyl} carbamoyl) cyclohexanecarboxylic acid and 2-(N-{(1S)-1-[N-((1S)-1-carbamoylpropyl)carbamoyl]-2-naphthylethyl}carbamoyl)(1S,2S)cyclohexanecarboxylic acid were prepared by stirring a mixture of trans-1,2-cyclohexanedicarboxylic anhydride (0.46g, 3mmol) and (2S)-N-((1S)-1-carbamoylpropyl)-2-amino-3-naphthylpropan amide (0.45g, 2mmol) in dichloromethane (10mL) for overnight. The dichloromethane was rotovaoped, the residue was taken in EtOAc and filtered. The solid was the 1/1 mixture of two diasteroismers. Yield: 0.50g (72%).

Mixture of Diastereo isomers (2S)-N-((1S)-1-carbamoylpropyl)-2-({(1S,2S)-2-[N-(phenylmethoxy)carbamoyl]cyclohexyl}-carbonylamino)-3-naphthylpropanamide was prepared from mixture of (1R,2R)-2-(N-{(1S)-1-[N-((1S)-1-carbamoylpropyl)

carbamoyl]-2-naphthylethyl} carbamoyl) cyclohexanecarboxylic acid and 2-(N-{(1S)-1-[N-((1S)-1-carbamoylpropyl)carbamoyl]-2-naphthylethyl}carbamoyl)(1S,2S) cyclo hexanecarboxylic acid (0.45g, 1mmol), O-benzylhydroxylamine (0.25g, 2mmol), EDC HCl (0.39g, 2mmol), HOBt (0.153g, 1mmol), DIEA (0.35mL, 2mmol), DMF (5mL) using the procedure from Example 3. Yield: 175mg (31%).

Mixture of 2-[(2-(N-hydroxycarbamoyl)(1S,2S)cyclohexyl)carbonylamino](2S)-N-((1S)-1-carbamoylpropyl)-3-naphthylpropanamide and 2-[(2-(N-hydroxycarbamoyl) (1R,2R)cyclohexyl)carbonylamino](2S)-N-((1S)-1-carbamoylpropyl)-3-naphthyl propanamide was prepared by stirring the mixture of Diastereo isomers (2S)-N-((1S)-1-carbamoylpropyl)-2-({(1S,2S)-2-[N-(phenylmethoxy)carbamoyl]cyclohexyl}-carbonylamino)-3-naphthylpropanamide (0.17g, 0.3mmol) in acetic acid (10mL) and 10% palladium/carbon (50mg) for overnight in presence of hydrogen. The next day, the palladium/carbon was filtered off and acetic was removed under vacuum to get a solid with faint orange color. Yield: 0.10g (71%). MS: ($M+H^+$) 469.

Example 126: Compound 128: 2-{(1E)-1-aza-2-[3-({5-[3-(3-methoxyphenoxy) phenyl](1,3,4-thiadiazol-2-yl)}amino)phenyl]prop-1-enyloxy}acetic acid

A mixture of 3-bromoanisole (10.00g, 53.5mmol), methyl 3-hydroxybenzoate (8.14g, 53.5mmol) and potassium carbonate (14.78g, 106.9mmol) in dry pyridine (75mL) were stirred under argon at room temperature. Copper (II) oxide (8.51g, 106.9mmol) was added and the reaction mixture refluxed for 65 hours. After cooling to room temperature the mixture was added CH_2Cl_2 (50mL) and filtered through celite. The filter cake was washed with fresh CH_2Cl_2 (50mL). The combined organics were concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate / hexanes, 1:10 to 1:4) to yield 8.77g (64%) of methyl 3-(3-methoxyphenoxy)benzoate as colorless oil.

Prepared in a manner similar to that described in Example 37 using 8.77g (34mmol) of methyl 3-(3-methoxyphenoxy)benzoate and 6.59mL (136mmol) of hydrazine hydrate to yield 8.25g (94%) of 1-(3-methoxyphenoxy)benzene-3-carbohydrazide.

Prepared in a manner similar to that described in Example 37 using 2.00g (7.70mmol) of 1-(3-methoxyphenoxy)benzene-3-carbohydrazide and 1.374g (7.70mmol) of 3-acetylphenyl isothiocyanate to yield 3.20g (95%) of N-({[(3-acetylphenyl)amino] thioxomethyl}amino)[3-(3-methoxyphenoxy)phenyl]carboxamide.

Prepared in a manner similar to that described in Example 37 using 3.20g (7.35mmol) of N-({[(3-acetylphenyl)amino]thioxomethyl}amino)[3-(3-methoxyphenoxy)phenyl] carboxamide and 2.95g (15.50mmol) of p-toluenesulfonic acid monohydrate (replace the conc.H_2SO_4) to yield 1.882g (61%) of 1-[3-({5-[3-(3-methoxyphenoxy)phenyl]-1,3,4-thiadiazol-2-yl}amino)phenyl]ethan-1-one. MS $(M+H)^+$ 418; $(M-H)^-$ 416.

Prepared in a manner similar to that described in Example 40 using 0.050g (0.12mmol) of 1-[3-({5-[3-(3-methoxyphenoxy)phenyl]-1,3,4-thiadiazol-2-yl}amino)phenyl]ethan-1-one, 0.018g (0.14mmol) of carboxymethoxylamine hemihydrochloride and 0.02mL (0.14mmol) of triethylamine to yield 0.011g (19%) of 2-{(1E)-1-aza-2-[3-({5-[3-(3-methoxyphenoxy)phenyl](1,3,4-thiadiazol-2-yl)}amino)phenyl]prop-1-enyloxy}acetic acid. MS $(M+H)^+$ 491; $(M-H)^-$ 489.

Example 127: Compound 129: 4-{[3-({5-[5-methoxy-3-(phenylmethoxy)phenyl]-1,3,4-thiadiazol-2-yl}amino)phenylthio]methyl}benzoic acid

3-aminothiophenol (1.1mL, 20mmol), methyl 4-(bromomethyl)benzoate (5.04g, 22mmol), 1M NaOH (25mL) in methanol (50mL) were stirred for 1 hour. Concentrated reaction mixure. The crude residue was purified by flash chromatography (hexanes/ ethyl acetate, 4:1) to yield 1.9g (32%) of methyl 4-[(3-aminophenylthio)methyl]benzoate as a white solid.

Methyl 4-[(3-aminophenylthio)methyl]benzoate (1.8g, 6.6mmol), dichloromethane (68mL), water (90mL), and thiophosgene (1.03mL, 13.4mmol) were stirred for 24 hours. Removed dichloromethane. Washed with water and extracted with dichloromethane.

Dried dichloromethane over sodium sulfate, filtered, and concentrated to yield 2g (96%) of methyl 4-[(3-isothiocyanatophenylthio)methyl]benzoate as a brown liquid. Following the procedure of Example 31, methyl 4-[(3-isothiocyanatophenylthio) methyl]benzoate (1.9g, 6mmol), (0.58mL, 12mmol), and toluene instead of ethanol to yield 790mg (38%) of methyl 4-({3-[(hydrazinothioxomethyl)amino]phenylthio} methyl)benzoate as a white solid.

Methyl 4-({3-[(hydrazinothioxomethyl)amino]phenylthio}methyl)benzoate (190mg, 0.54mmol) and 3-methoxy-5-(phenylmethoxy)benzaldehyde (190mg, 0.54mmol) in ethanol were reluxed for 4 hours to yield 199mg (65%) of methyl 4-[(3-{[({(1E)-1-aza-2-[5-methoxy-3-(phenylmethoxy) phenyl]vinyl}amino)thioxomethyl] amino}phenylthio) methyl]benzoate as a white solid.

Following the procedure of Example 32, methyl 4-[(3-{[({(1E)-1-aza-2-[5-methoxy-3-(phenylmethoxy)phenyl]vinyl}amino)thioxomethyl]amino}phenylthio)methyl]benzoate (176mg, 0.3mmol) to yield 103mg (61%) of methyl 4-{[3-({5-[5-methoxy-3-(phenylmethoxy)phenyl]-1,3,4-thiadiazol-2-yl}amino)phenylthio]methyl}benzoate as a light brown solid.

Following the procedure of Example 34, methyl 4-{[3-({5-[5-methoxy-3-(phenylmethoxy)phenyl]-1,3,4-thiadiazol-2-yl}amino)phenylthio]methyl}benzoate (30mg, 0.05mmol) to the isolation of 4-{[3-({5-[5-methoxy-3-(phenylmethoxy)phenyl]-1,3,4-thiadiazol-2-yl}amino)phenylthio]methyl}benzoic acid (25mg) in 93% yield, R_f = 0.44 (chloroform/methanol/acetic acid, 85:10:5). MS $(M+H)^+$556.

Example 128: Compound 130: 2-((1E)-1-aza-2-{3-[aza(3-methyl-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]phenyl} prop-1-enyloxy)acetic acid

1-{3-[aza(3-methyl-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]phenyl}ethan-1-one was prepared from 1-{3-[(5-{3-[3-(trifluoromethyl) phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]phenyl}ethan-1-one (0.20g, 0.45mmol),

1M solution of potassium tert-butoxide (0.45mL, 0.45mmol), methyliodide (0.28mL, 4.5mmol) using the procedure from Example 38. Yield: 15mg (7%).

2-((1E)-1-aza-2-{3-[aza(3-methyl-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]phenyl}prop-1-enyloxy)acetic acid was prepared from 1-{3-[aza(3-methyl-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene)) methyl]phenyl}ethan-1-one (20mg, 0.043mmol), carboxymethoxylamine hemihydrochloride (11mg, 0.09mmol) , triethylamine (7μL, 0.05mmol) and ethanol (2mL) using the procedure from Example 41. Yield: 16mg (70%).
MS: $(M+H^+)$ 543 and $(M-H)^-$ 541.

Example 129: Compound 131: 3-({5-[5-({3-[(4-carboxyphenyl)methylthio]phenyl} amino)(1,3,4-thiadiazol-2-yl)]-3-(phenylmethoxy)phenoxy}methyl)benzoic acid

Methyl 4-({3-[(hydrazinothioxomethyl)amino]phenylthio}methyl)benzoate (223mg, 0.75mmol) and methyl 3-{[5-carbonyl-3-(phenylmethoxy)phenoxy]methyl}benzoate (282mg, 0.75mmol) in ethanol were reluxed for overnight to yield 529mg (99%) of methyl 3-({3-[(1E)-2-aza-2-({[(3-{[4-(methoxycarbonyl)phenyl]methylthio}phenyl) amino]thioxomethyl}amino)vinyl]-5-(phenylmethoxy)phenoxy}methyl)benzoate as a brown liquid.

Following the procedure of Example 32, methyl 3-({3-[(1E)-2-aza-2-({[(3-{[4-(methoxycarbonyl)phenyl]methylthio}phenyl)amino]thioxomethyl}amino)vinyl]-5-(phenylmethoxy)phenoxy}methyl)benzoate (529mg, 0.75mmol) to yield 112mg (21%) of methyl 3-[(5-{5-[(3-{[4-(methoxycarbonyl)phenyl]methylthio}phenyl)amino](1,3,4-thiadiazol-2-yl)}-3-(phenylmethoxy)phenoxy)methyl]benzoate as an off white solid.

Following the procedure of Example 34, methyl 3-[(5-{5-[(3-{[4-(methoxycarbonyl) phenyl]methylthio}phenyl)amino](1,3,4-thiadiazol-2-yl)}-3-(phenylmethoxy)phenoxy) methyl]benzoate (100mg, 0.14mmol). The crude residue was recrystallized in ethanol to the isolation of 3-({5-[5-({3-[(4-carboxyphenyl)methylthio]phenyl} amino)(1,3,4-

thiadiazol-2-yl)]-3-(phenylmethoxy)phenoxy}methyl)benzoic acid (34mg) in 36% yield. R_f = 0.69 (chloroform/methanol/acetic acid, 85:10:5). MS (M+H)$^-$674.

Example 130: Compound 132: 4-({5-[3,5-bis(phenylmethoxy)phenyl]-1,3,4-thiadiazol-2-yl}amino)benzoic acid

Following the procedure of Example 31, 4-methoxycarbonylphenyl isothiocyanate (193mg, 1mmol), hydrazine hydrate (0.097mL, 2mmol), and using toluene instead of ethanol to yield 192mg (85%) of methyl 4-[(hydrazinothioxomethyl)amino]benzoate as a white solid.

Methyl 4-[(hydrazinothioxomethyl)amino]benzoate (180mg, 0.8mmol) and 3,5-dibenzyloxybenzaldehyde (254mg, 0.8mmol) in ethanol were reluxed for 2 hours. As the reaction was cooled, precipitate formed to yield 302mg (72%) of methyl 4-{[({(1E)-1-aza-2-[3,5-bis(phenylmethoxy)phenyl]vinyl}amino)thioxomethyl]amino}benzoate as a white solid.

Following the procedure of Example 32, methyl 4-{[({(1E)-1-aza-2-[3,5-bis(phenylmethoxy)phenyl]vinyl}amino)thioxomethyl]amino}benzoate (289mg, 0.55mmol) to yield 225mg (78%) of methyl 4-({5-[3,5-bis(phenylmethoxy)phenyl]-1,3,4-thiadiazol-2-yl}amino)benzoate as a light brown solid.

Following the procedure of Example 34, methyl 4-({5-[3,5-bis(phenylmethoxy)phenyl]-1,3,4-thiadiazol-2-yl}amino)benzoate (209mg, 0.4mmol) to the isolation of 4-({5-[3,5-bis(phenylmethoxy)phenyl]-1,3,4-thiadiazol-2-yl}amino)benzoic acid (93mg) in 97% yield, R_f = 0.22 (ethyl acetate/ hexanes, 1:1). MS (M+H)$^-$509.

Example 131: Compound 133: 1-({4-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]phenyl} carbonyl)piperidine-4-carboxylic acid

Ethyl 1-({3-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino] phenyl} carbonyl)piperidine-4-carboxylate was prepared from 3-[(5-{3-[3-

(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]benzoic acid (70mg, 0.15mmol), ethyl isonipecotate (24mg, 0.15mmol), EDC HCl (35mg, 0.18mmol), HOBt (21mg, 0.15mmol), DIEA (26µl 0.15mmol) dichloromethane (2.0mL) using the procedure from Example 3. Yield: 73mg (80%).

1-({4-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]phenyl} carbonyl)piperidine-4-carboxylic acid was prepared by saponification of ethyl 1-({3-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino] phenyl} carbonyl) piperidine-4-carboxylate (76mg, 0.13mmol) and lithiumhydroxide (3mg, 0.13mmol) using the procedure from Example 34. Yield: 24mg (33%).
MS: $(M+H^+)$ 591 and $(M-CF_3CO_2)^-$ 681.

Example 132: Compound 135: 3-{[3-(5-{[3-(5-carboxypentylthio)phenyl]amino} (1,3,4-thiadiazol-2-yl))-5-(phenylmethoxy)phenoxy]methyl}benzoic acid

3-aminothiophenol (1.7mL, 16mmol), ethyl 6-bromohexanoate (3.6g, 16mmol), 1M NaOH (16mL) in ethanol (30mL) were stirred for thirty minutes. Concentrated reaction mixure. The crude residue was washed with 0.1N NaOH and extracted with ethyl acetate. Ethyl acetate layer was washed with water, brine, dried over sodium sulfate, filtered, and concentrated. The crude residue was purified by flash chromatography (hexanes/ ethyl acetate, 9:1) to yield 2g (48%) of ethyl 6-(3-aminophenylthio)hexanoate as a yellow solid.

Ethyl 6-(3-aminophenylthio)hexanoate (1.8g, 6.7mmol), dichloromethane (68mL), water (90mL), and thiophosgene (1.03mL, 13.4mmol) were stirred for 24 hours. Removed dichloromethane. Washed with water and extracted with dichloromethane. Dried dichloromethane over sodium sulfate, filtered, and concentrated to yield 2g (97%) of ethyl 6-(3-isothiocyanatophenylthio)hexanoate as a brown liquid.

Following the procedure of Example 31, ethyl 6-(3-isothiocyanatophenylthio)hexanoate (1.5g, 4.8mmol), hydrazine hydrate (0.47mL, 9.7mmol), and toluene instead of ethanol to

yield 1.65g (99%) of ethyl 6-{3-[(hydrazinothioxomethyl)amino]phenylthio}hexanoate as a yellow solid.

Ethyl 6-{3-[(hydrazinothioxomethyl)amino]phenylthio}hexanoate (225mg, 0.75mmol) and methyl 3-{[5-carbonyl-3-(phenylmethoxy)phenoxy]methyl}benzoate (282mg, 0.75mmol) in ethanol were reluxed for 3 hours to yield 500mg (95%) of ethyl 6-{3-[({[(1E)-1-aza-2-(5-{[3-(methoxycarbonyl)phenyl]methoxy}-3-(phenylmethoxy)phenyl) vinyl]amino}thioxomethyl)amino]phenylthio}hexanoate as a yellowish brown solid.

Following the procedure of Example 32, ethyl 6-{3-[({[(1E)-1-aza-2-(5-{[3-(methoxycarbonyl)phenyl]methoxy}-3-(phenylmethoxy)phenyl)vinyl]amino} thioxomethyl)amino]phenylthio}hexanoate (490mg, 0.7mmol). The crude residue was purified by flash chromatography (ethyl acetate/hexanes, 1:1) to yield 71mg (14%) of ethyl 6-(3-{[5-(3-{[3-(methoxycarbonyl)phenyl]methoxy}-5-(phenylmethoxy)phenyl)-1,3,4-thiadiazol-2-yl]amino}phenylthio)hexanoate as an off white solid.

Following the procedure of Example 34, ethyl 6-(3-{[5-(3-{[3-(methoxycarbonyl) phenyl]methoxy}-5-(phenylmethoxy)phenyl)-1,3,4-thiadiazol-2-yl]amino}phenylthio) hexanoate (100mg, 0.14mmol) to the isolation of 3-{[3-(5-{[3-(5-carboxypentylthio) phenyl]amino}(1,3,4-thiadiazol-2-yl))-5-(phenylmethoxy)phenoxy]methyl}benzoic acid (38mg) in 41% yield, $R_f = 0.53$ (chloroform/methanol/acetic acid, 85:10:5).
MS $(M+H)^-$ 653.

Example 133: Compound 137: 3-[(5-{3,5-bis[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]butanoic acid

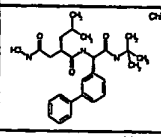
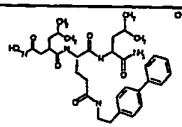
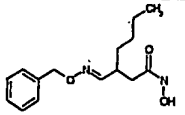
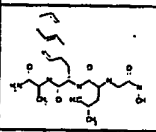
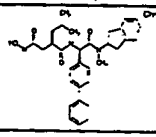
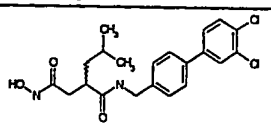
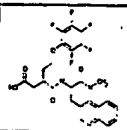
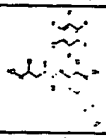
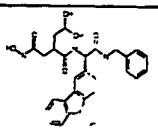
Prepared in a manner similar to that described in Compound 128 using 10.00g (59.4mmol) of methyl 3,5-dihydroxybenzoate, 8.4mL (59.4mmol) of 3-bromobenzotrifluoride, 16.44g (118.8mmol) of potassium carbonate and 9.46g (118.8mmol) of Copper (II) oxide to yield 4.77g (18%) of methyl 3,5-bis[3-

(trifluoromethyl)phenoxy]benzoate and 3.00g (16%) of methyl 5-oxy-3-[3-(trifluoromethyl)phenoxy]benzoate.

Prepared in a manner similar to that described in Example 37 using 4.77g (10.5mmol) of methyl 3,5-bis[3-(trifluoromethyl)phenoxy]benzoate and 0.76mL (15.7mmol) of hydrazine hydrate to yield 4.35g (91%) of 3,5-bis[3-(trifluoromethyl)phenoxy] benzenecarbohydrazide.

Prepared in a manner similar to that described in Example 37 using 0.300g (0.66mmol) of 3,5-bis[3-(trifluoromethyl)phenoxy]benzenecarbohydrazide and 0.114g (0.66mmol) of ethyl 3-isothiocyanatobutyrate to yield 0.138g (34%) of ethyl 3-[(5-{3,5-bis[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]butanoate.

Prepared in a manner similar to that described in Example 35 using 0.040g (0.065mmol) of ethyl 3-[(5-{3,5-bis[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino] butanoate to yield 0.032g (84%) of 3-[(5-{3,5-bis[3-(trifluoromethyl) phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]butanoic acid. MS $(M+Na)^+$ 606; $(M-H)^-$ 582.

Compound number	Structure	Chemical name	LF activity code*	MMP1 activity code*
1		methyl (3R)-3-(N-{[N-(tert-butyl)carbamoyl](3-phenylphenyl)methyl}carbamoyl)-5-methylhexanoate	C	E
2		2-[2-(N-hydroxycarbamoylmethyl)(2R)-4-methylpentanoylamino](2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-N'-[2-(4-phenylphenyl)ethyl]pentane-1,5-diamide	D	D
3		3-(Benzyloxyimino-methyl)-heptanoic acid hydroxyamide	A	
4		2-[(N-hydroxycarbamoylmethyl)amino](2S)-N-{(1S)-1-[N-((1S)-1-carbamoylethyl)carbamoyl]-2-(2-naphthyl)ethyl}-4-methylpentanamide	A	
5		2-(N-hydroxycarbamoylmethyl)(2R)-N-[(N-indan-2-yl-N-methylcarbamoyl)(4-phenylphenyl)methyl]-4-methylpentanamide	C	
6		2-(N-hydroxycarbamoylmethyl)-N-{[4-(3,4-dichlorophenyl)phenyl]methyl}-4-methylpentanamide	B	B
7		3-{N-[(1S)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl]carbamoyl}-5-(2,3,4,5,6-pentafluorophenoxy)pentanoic acid	A	
8		2-(N-hydroxycarbamoylmethyl)-N-[(1S)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl]-4-(2,3,4,5,6-pentafluorophenoxy)butanamide	A	
9		2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-{(9-methylcarbazol-3-yl)[N-benzylcarbamoyl]methyl}pentanamide	E	E

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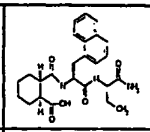
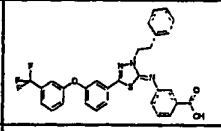
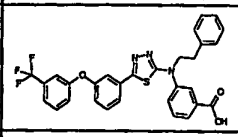
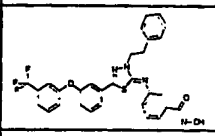
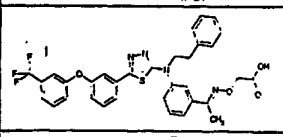
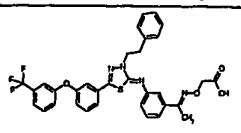
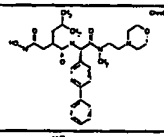
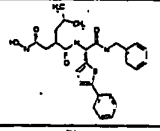
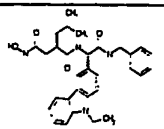
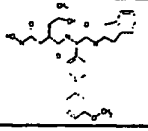
10		Mixture of 2-(N-{(1S)-1-[N-((1S)-1-carbamoylpropyl)carbamoyl]-2-naphthylethyl}carbamoyl)(1S,2S)cyclohexanecarboxylic acid and(1R,2R)-2-(N-{(1S)-1-[N-((1S)-1-carbamoylpropyl)carbamoyl]-2-naphthylethyl}carbamoyl)cyclohexanecarboxylic acid	A	
11		3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]benzoic acid	B	
12		3-[(2-phenylethyl)(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazol 2-yl))amino]benzoic acid	B	
13		1-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]benzene-3-carbohydroxamic acid	A	
14		2-((1E)-1-aza-2-{3-[(2-phenylethyl)(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazol-2-yl))amino]phenyl}prop-1-enyloxy)acetic acid	C	
15		2-((1E)-1-aza-2-{3-[aza(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]phenyl}prop-1-enyloxy)acetic acid	B	
16		N1-{Biphenyl-4-yl-[methyl-(2-morpholin-4-yl-ethyl)-carbamoyl]-methyl}-N4-hydroxy-2-isobutyl-succinamide	C	
17		2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-{(5-phenyl(2-thienyl))[N-benzylcarbamoyl]methyl}pentanamide	E	
18		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(9-ethylcarbazol-3-yl)[N-benzylcarbamoyl]methyl}-4-methylpentanamide	E	
19		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(N-indan-2-ylcarbamoyl)[4-(3-methoxyphenyl)phenyl]methyl}-4-methylpentanamide	D	

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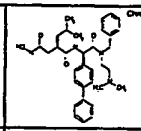
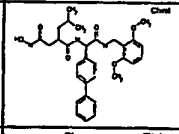
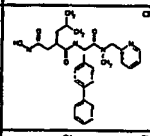
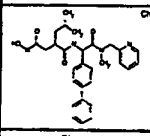
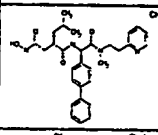
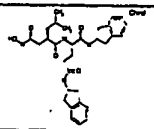
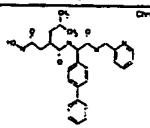
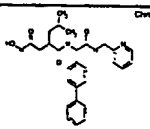
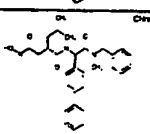
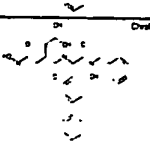
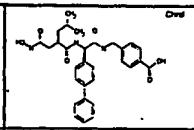
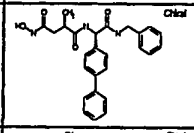
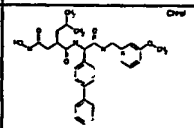
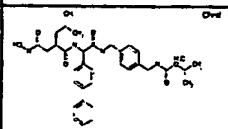
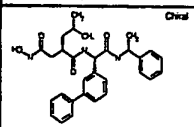
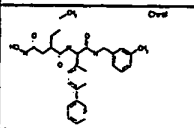
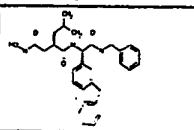
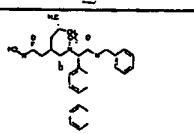
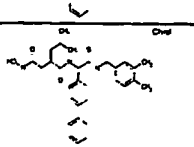
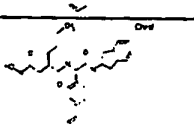
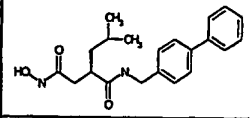
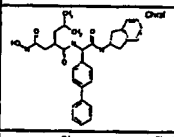
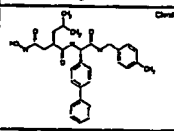
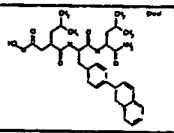
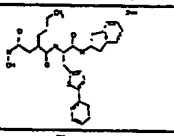
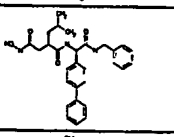
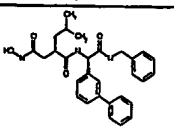
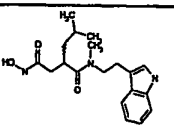
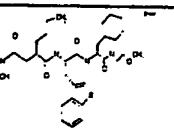
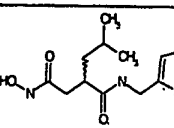
20		2-(N-hydroxycarbamoylmethyl)(2R)-N-((1R){N-[2-(dimethylamino)ethyl]-N-benzylcarbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide	D	
21		2-(N-hydroxycarbamoylmethyl)(2R)-N-({N-[(2,6-dimethoxyphenyl)methyl]carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide	D	D
22		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)[N-methyl-N-(2-pyridylmethyl)carbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide	D	E
23		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)[N-methyl-N-(2-pyridylmethyl)carbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide	D	
24		2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-{[N-methyl-N-(2-(2-pyridyl)ethyl)carbamoyl](4-phenylphenyl)methyl}pentanamide	C	D
25		2-[2-(N-hydroxycarbamoylmethyl)(2R)-4-methylpentanoylamino](2S)-N-indan-2-yl-N'-indan-2-ylpentane-1,5-diamide	C	E
26		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)(4-phenylphenyl)[N-(2-pyridylmethyl)carbamoyl]methyl}-4-methylpentanamide	D	D
27		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)(4-phenylphenyl)[N-(2-pyridylmethyl)carbamoyl]methyl}-4-methylpentanamide	D	E
28		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)[N-methyl-N-benzylcarbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide	C	D
29		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)[N-methyl-N-benzylcarbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide	D	D

30		4-({2-[2-(N-hydroxycarbamoylmethyl)(2R)-4-methylpentanoylamino]-2-(4-phenylphenyl)acetylamino}methyl)benzoic acid	C	E
31		3-(N-hydroxycarbamoyl)(2R)-2-methyl-N-{[N-benzylcarbamoyl](4-phenylphenyl)methyl}propanamide	D	E
32		2-(N-hydroxycarbamoylmethyl)(2R)-N-({N-[(3-methoxyphenyl)methyl]carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide	D	E
33		2-(N-hydroxycarbamoylmethyl)(2R)-N-({N-[(4-{[(tert-butoxy)carbonylamino]methyl}phenyl)methyl]carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide	C	E
34		2-(N-hydroxycarbamoylmethyl)(2R)-N-{[N-((1S)-1-phenylethyl)carbamoyl](3-phenylphenyl)methyl}-4-methylpentanamide	D	F
35		2-(N-hydroxycarbamoylmethyl)(2R)-N-({N-[(3-methylphenyl)methyl]carbamoyl}(4-phenylphenyl)methyl)hexanamide	C	E
36		2-(N-hydroxycarbamoylmethyl)(2R)-N-{fluoren-2-yl[N-benzylcarbamoyl]methyl}-4-methylpentanamide	E	E
37		2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-methyl-N-{[N-benzylcarbamoyl](4-phenylphenyl)methyl}pentanamide	C	D
38		2-(N-hydroxycarbamoylmethyl)(2R)-N-({N-[(3,4-dimethylphenyl)methyl]carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide	D	E
39		2-(N-hydroxycarbamoylmethyl)(2R)-N-[(N-indan-2-ylcarbamoyl)(4-phenylphenyl)methyl]hexanamide	D	E

40		2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-[(4-phenylphenyl)methyl]pentanamide	C	D
41		2-(N-hydroxycarbamoylmethyl)(2R)-N-[(R,S)-(N-indan-2-ylcarbamoyl)(4-phenylphenyl)methyl]-4-methylpentanamide	E	D
42		2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-({N-[(4-methylphenyl)methyl]carbamoyl}(4-phenylphenyl) methyl)pentanamide	D	E
43		2-(N-hydroxycarbamoylmethyl)(2R)-N-{1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-(4-(2-naphthyl)phenyl)ethyl}-4-methylpentanamide	D	E
44		2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-1-(N-indan-2-ylcarbamoyl)-2-(5-phenyl(2-thienyl))ethyl]hexanamide	D	F
45		2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-{[N-benzylcarbamoyl](4-phenylphenyl)methyl}pentanamide	E	E
46		2-(N-hydroxycarbamoylmethyl)(2R)-4-methyl-N-{[N-benzylcarbamoyl](3-phenylphenyl)methyl}pentanamide	E	F
47		2-(N-hydroxycarbamoylmethyl)-N-(2-indol-3-ylethyl)-4-methyl-N-methylpentanamide	C	C
48		2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-1-(N-{(1S)-2-cyclohexyl-1-[N-(2-methoxyethyl)carbamoyl]ethyl}carbamoyl)-2-benzo[b]thiophen-3-ylethyl]hexanamide	D	E
49		2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(5-(2-thienyl)(2-thienyl))methyl]pentanamide	B	C

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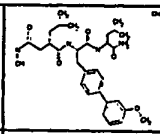
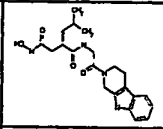
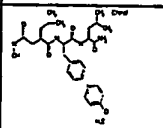
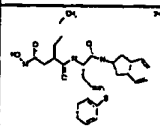
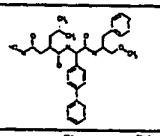
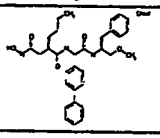
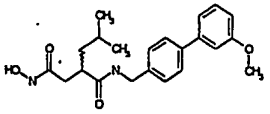
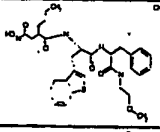
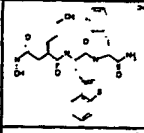
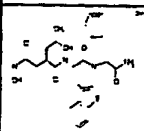
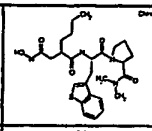
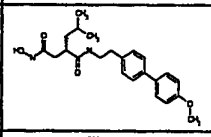
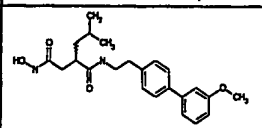
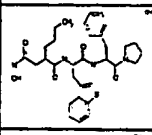
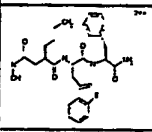
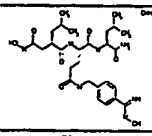
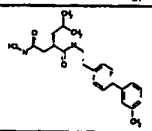
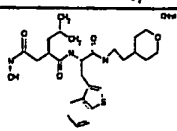
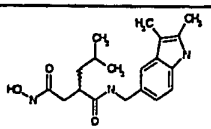
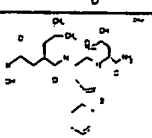
50		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-[4-(3-methoxyphenyl)phenyl]ethyl}-4-methylpentanamide	D	E
51		2-(N-hydroxycarbamoylmethyl)-4-methyl-N-(2-oxo-2-(1,2,3,4-tetrahydrobeta-carbolin-2-yl)ethyl)pentanamide	B	E
52		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-[4-(4-methoxyphenyl)phenyl]ethyl}-4-methylpentanamide	D	D
53		2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-2-benzo[b]thiophen-3-yl-1-(N-indan-2-ylcarbamoyl)ethyl]hexanamide	D	F
54		2-(N-hydroxycarbamoylmethyl)(2R)-N-((1R){N-[(1S)-2-methoxy-1-benzylethyl]carbamoyl}(4-phenylphenyl)methyl)-4-methylpentanamide	C	C
55		2-(N-hydroxycarbamoylmethyl)(2R)-N-((1S){N-[(1S)-2-methoxy-1-benzylethyl]carbamoyl}(4-phenylphenyl)methyl)hexanamide	D	D
56		2-(N-hydroxycarbamoylmethyl)-N-{[4-(3-methoxyphenyl)phenyl]methyl}-4-methylpentanamide	B	C
57		2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-1-(N-{(1S)-1-[N-(2-methoxyethyl)carbamoyl]-2-phenylethyl}carbamoyl)-2-benzo[b]thiophen-3-ylethyl]hexanamide	D	
58		2-(N-hydroxycarbamoylmethyl)(2R)-N-{1-[N-((1R)-1-carbamoyl-2-phenylethyl)carbamoyl](1S)-2-benzo[b]thiophen-3-ylethyl}hexanamide	D	
59		2-(N-hydroxycarbamoylmethyl)(2R)-N-{1-[N-((1R)-1-carbamoyl-2-phenylethyl)carbamoyl](1S)-2-benzo[b]thiophen-3-ylethyl}-4-methylpentanamide	C	E

60		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-2-[(2S)-2-(N,N-dimethylcarbamoyl)pyrrolidinyl]-1-(benzo[b]thiophen-3-ylmethyl)-2-oxoethyl}hexanamide	B	E
61		N'-methoxy-N-{2-[4-(4-methoxyphenyl)phenyl]ethyl}-2-(2-methylpropyl)butane-1,4-diamide	B	C
62		N'-methoxy-N-{2-[4-(3-methoxyphenyl)phenyl]ethyl}-2-(2-methylpropyl)butane-1,4-diamide	B	C
63		2-(N-hydroxycarbamoylmethyl)(2R)-N-((1S)-1-{N-[(1S)-2-oxo-1-benzyl-2-pyrrolidinylethyl]carbamoyl}-2-benzo[b]thiophen-3-ylethyl)hexanamide	C	E
64		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-phenylethyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}hexanamide	D	F
65		2-[2-(N-hydroxycarbamoylmethyl)-4-methylpentanoylamino](2S)-N-((1S)-1-carbamoyl-3-methylbutyl)-N'-{[4-((hydroxyamino)iminomethyl)phenyl]methyl}pentane-1,5-diamide	C	D
66		2-(N-hydroxycarbamoylmethyl)-4-methyl-N-{2-[4-(3-methylphenyl)phenyl]ethyl}pentanamide	B	C
67		2-(N-hydroxycarbamoylmethyl)-N-{(1S)-2-benzo[b]thiophen-3-yl-1-[N-(2-(2H-3,4,5,6-tetrahydropyran-4-yl)ethyl)carbamoyl]ethyl}-4-methylpentanamide	C	
68		2-(N-hydroxycarbamoylmethyl)-N-[(2,3-dimethylindol-5-yl)methyl]-4-methylpentanamide	B	C
69		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}-4-methylpentanamide	C	D

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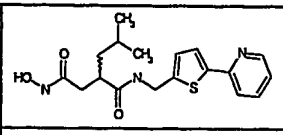
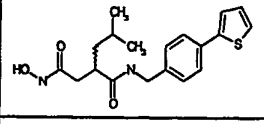
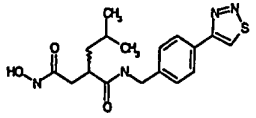
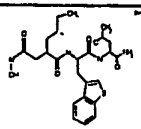
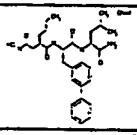
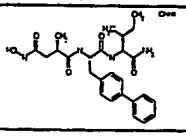
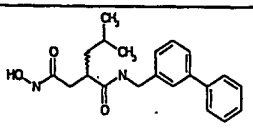
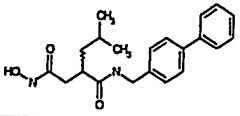
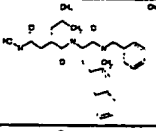
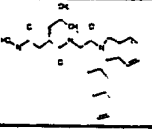
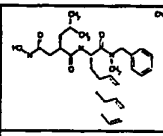
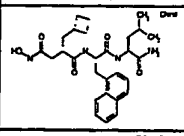
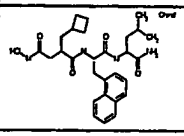
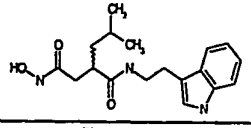
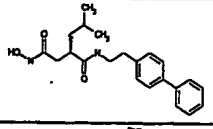
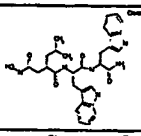
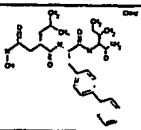
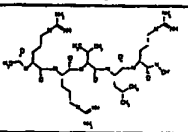
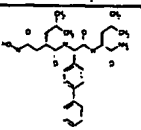
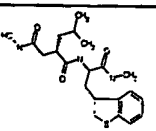
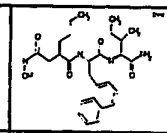
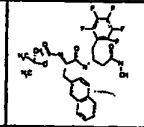
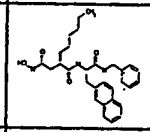
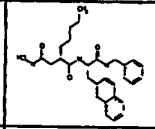
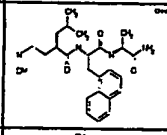
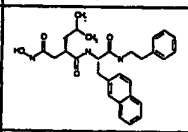
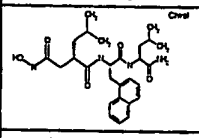
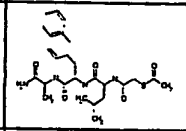
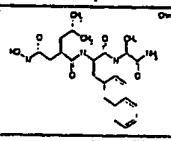
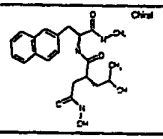
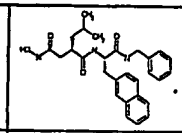
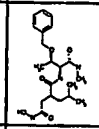
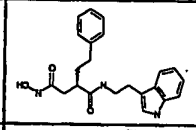
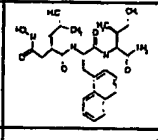
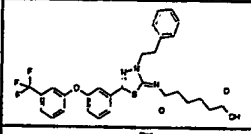
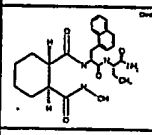
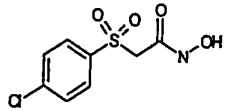
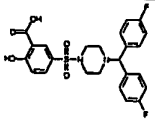
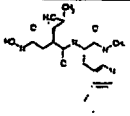
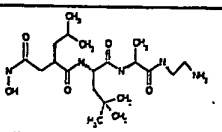
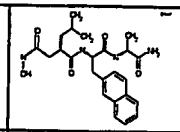
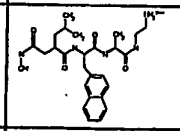
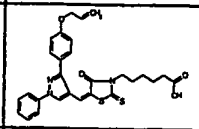
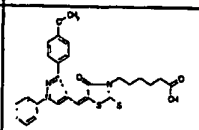
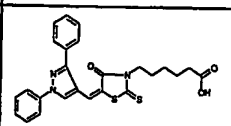
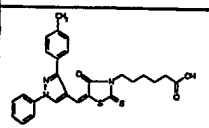
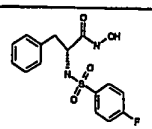
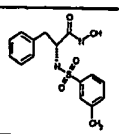
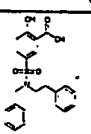
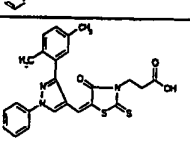
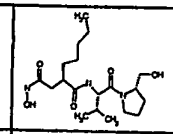
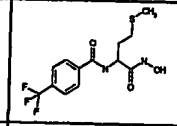
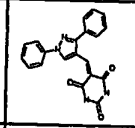
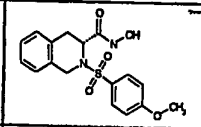
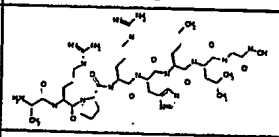
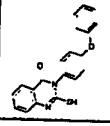
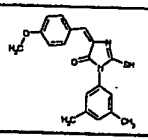
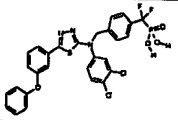
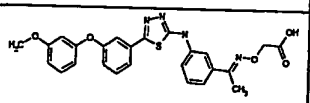
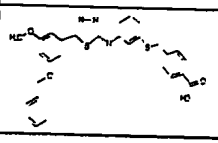
70		2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(5-(2-pyridyl)(2-thienyl))methyl]pentanamide	B	C
71		2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(4-(2-thienyl)phenyl)methyl]pentanamide	B	C
72		2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(4-(1,2,3-thiadiazol-4-yl)phenyl)methyl]pentanamide	B	C
73		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-benzo[b]thiophen-3-ylethyl}hexanamide	D	E
74		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-(3-phenylphenyl)ethyl}hexanamide	C	E
75		3-(N-hydroxycarbamoyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-(4-phenylphenyl)ethyl}-2-methylpropanamide	B	B
76		2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(3-phenylphenyl)methyl]pentanamide	B	C
77		2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[(4-phenylphenyl)methyl]pentanamide	C	C
78		2-(N-hydroxycarbamoylmethyl)(2S)-N-{(1S)-1-[N-methyl-N-benzylcarbamoyl]-2-(2-naphthyl)ethyl}-4-methylpentanamide	A	C
79		2-(N-hydroxycarbamoylmethyl)-N-[(1S)-2-isoindolin-2-yl-1-(2-naphthylmethyl)-2-oxoethyl]-4-methylpentanamide	C	D

80		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-methyl-N-benzylcarbamoyl]-2-(2-naphthyl)ethyl}-4-methylpentanamide	C	E
81		3-(N-hydroxycarbamoyl)(2S)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl}-2-(cyclobutylmethyl)propanamide	B	D
82		3-(N-hydroxycarbamoyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl}-2-(cyclobutylmethyl)propanamide	D	E
83		2-(N-hydroxycarbamoylmethyl)-N-(2-indol-3-ylethyl)-4-methylpentanamide	B	C
84		2-(N-hydroxycarbamoylmethyl)-4-methyl-N-[2-(4-phenylphenyl)ethyl]pentanamide	B	C
85		2-(N-hydroxycarbamoylmethyl)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-indol-3-ylethyl) carbamoyl]-2-indol-3-ylethyl}-4-methylpentanamide	C	E
86		2-(N-hydroxycarbamoylmethyl)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-(4-phenylphenyl)ethyl}-4-methylpentanamide	D	E
87		Ac-Arg-Arg-Val-Leu-Arg-NHOH	C	B
88		2-(N-hydroxycarbamoylmethyl)-N-{(1S)[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl](4-phenylphenyl)methyl}-4-methylpentanamide	D	D
89		2-(N-hydroxycarbamoylmethyl)-N-[2-benzo[b]thiophen-3-yl-1-(N-methylcarbamoyl)ethyl]-4-methylpentanamide	B	F

90		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S,2S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-naphthylethyl}hexanamide	D	E
91		N-{2-(N-hydroxycarbamoyl)(1R)-1-[(2,3,4,5,6-pentafluorophenyl)methyl]ethyl}(2R)-2-[(tert-butoxy)carbonylamino]-3-(2-naphthyl)propanamide	A	
92		2-(N-hydroxycarbamoylmethyl)-N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl]ethyl}octanamide	A	E
93		2-(N-hydroxycarbamoylmethyl)-N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl]ethyl}heptanamide	B	F
94		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoylethyl)carbamoyl]-2-naphthylethyl}-4-methylpentanamide	C	F
95		2-(N-hydroxycarbamoylmethyl)-N-{(1S)-2-(2-naphthyl)-1-[N-(2-phenylethyl)carbamoyl]ethyl}-4-methylpentanamide	C	F
96		2-(N-hydroxycarbamoylmethyl)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl)carbamoyl]-2-naphthylethyl}-4-methylpentanamide	C	D
97			A	
98		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)-1-[N-((1S)-1-carbamoylethyl)carbamoyl]-2-(2-naphthyl)ethyl}-4-methylpentanamide	A	D
99		2-(N-hydroxycarbamoylmethyl)-N-[(1S)-1-(N-methylcarbamoyl)-2-(2-naphthyl)ethyl]-4-methylpentanamide	A	E

100		2-(N-hydroxycarbamoylmethyl)-N-{(1S)-2-(2-naphthyl)-1-[N-benzylcarbamoyl]ethyl}-4-methylpentanamide	C	F
101		2-(N-hydroxycarbamoylmethyl)-N-[(1S,2R)-1-(N-methylcarbamoyl)-2-(phenylmethoxy)propyl]-4-methylpentanamide	A	D
102		2-(N-hydroxycarbamoylmethyl)-N-(2-indol-3-ylethyl)-4-phenylbutanamide	B	B
103		2-(N-hydroxycarbamoylmethyl)-N-{(1S)-1-[N-((1S)-1-carbamoyl-2-methylbutyl)carbamoyl]-2-naphthylethyl}-4-methylpentanamide	C	E
104		7-aza-6-oxo-7-(3-(2-phenylethyl)-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))heptanoic acid	B	
105		MIXTURE OF 2-[(2-(N-hydroxycarbamoyl)(1S,2S)cyclohexyl)carbonylamino](2S)-N-((1S)-1-carbamoylpropyl)-3-naphthylpropanamide and 2-[(2-(N-hydroxycarbamoyl)(1R,2R)cyclohexyl)carbonylamino](2S)-N-	A	
106		2-(4-Chloro-benzenesulfonyl)-N-hydroxy-acetamide	B	
107		5-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazine-1-sulfonyl}-2-hydroxy-benzoic acid	B	B
108		2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-2-indol-3-yl-1-(N-methylcarbamoyl)ethyl]-4-methylpentanamide	C	
109		2-[2-(N-hydroxycarbamoylmethyl)(2R)-4-methylpentanoylamino](2S)-N-{(1S)-1-[N-(2-aminoethyl)carbamoyl]ethyl}-4,4-dimethylpentanamide	B	

110		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1S)-1-[N-((1S)-1-carbamoylethyl)carbamoyl]-2-(2-naphthyl)ethyl}-4-methylpentanamide	C	
111		2-(N-hydroxycarbamoylmethyl)(2R)-N-[(1S)-1-(N-{(1S)-1-[N-(2-aminoethyl)carbamoyl]ethyl}carbamoyl)-2-(2-naphthyl)ethyl]-4-methylpentanamide	C	F
112		6-(4-oxo-5-{[1-phenyl-3-(4-prop-2-enyloxyphenyl)pyrazol-4-yl]methylene}-2-thioxo-1,3-thiazolidin-3-yl)hexanoic acid	B	
113		6-(5-{[3-(4-methoxyphenyl)-1-phenylpyrazol-4-yl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)hexanoic acid	B	
114		6-{5-[(1,3-diphenylpyrazol-4-yl)methylene]-4-oxo-2-thioxo-1,3-thiazolidin-3-yl}hexanoic acid	B	
115		6-(5-{[3-(4-methylphenyl)-1-phenylpyrazol-4-yl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)hexanoic acid	C	
116		(2R)-2-{[(4-fluorophenyl)sulfonyl]amino}-3-phenylpropanehydroxamic acid	B	
117		(2R)-2-{[(3-methylphenyl)sulfonyl]amino}-3-phenylpropanehydroxamic acid	B	
118		2-hydroxy-5-{[(2-phenylethyl)benzylamino]sulfonyl}benzoic acidi	B	
119		3-(5-{[3-(2,5-dimethylphenyl)-1-phenylpyrazol-4-yl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acids	B	

120		2-(N-hydroxycarbamoylmethyl)(2R)-N-{(1R)-2-[(2R)-2-(hydroxymethyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}heptanamide	B	E
121		N-(1-(N-hydroxycarbamoyl)-3-methylthiopropyl)[4-(trifluoromethyl)phenyl]carboxamide	B	
122		5-[(1,3-diphenylpyrazol-4-yl)methylene]-1,3-dihydropyrimidine-2,4,6-trionee	B	
123		(3R)-2-[(4-methoxyphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline-3-carbohydroxamic acid	B	
124		H-Ala-Arg-Pro-Arg-His-Nle-Leu-Gly-NHOH	B	
125		3-(4-phenoxyphenyl)-2-sulfanyl-3-hydroquinazolin-4-one	B	
126		1-(3,5-dimethylphenyl)-4-[(4-methoxyphenyl)methylene]-2-sulfanyl-1,3-diazolin-5-one	B	
127		{[4-({(3,4-Dichloro-phenyl)-[5-(3-phenoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-amino}-methyl)-phenyl]-difluoro-methyl}-phosphonic acid	B	
128		2-{(1E)-1-aza-2-[3-({5-[3-(3-methoxyphenoxy)phenyl](1,3,4-thiadiazol-2-yl)}amino)phenyl]prop-1-enyloxy}acetic acid	B	
129		4-{[3-({5-[5-methoxy-3-(phenylmethoxy)phenyl]-1,3,4-thiadiazol-2-yl}amino)phenylthio]methyl}benzoic acid	B	

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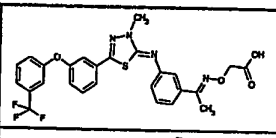
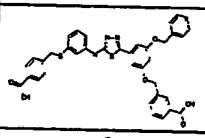
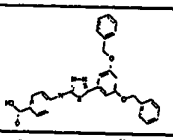
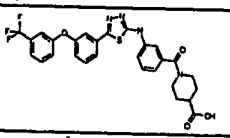
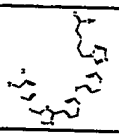
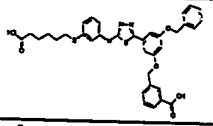
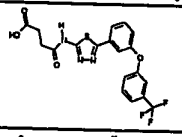
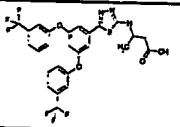
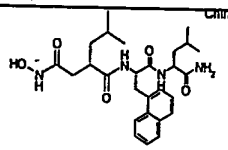
130		2-((1E)-1-aza-2-{3-[aza(3-methyl-5-{3-[3-(trifluoromethyl)phenoxy]phenyl}(1,3,4-thiadiazolin-2-ylidene))methyl]phenyl}prop-1-enyloxy)acetic acid	C	
131		3-({5-[5-({3-[(4-carboxyphenyl)methylthio]phenyl}amino)(1,3,4-thiadiazol-2-yl)]-3-(phenylmethoxy)phenoxy}methyl)benzoic acid	C	
132		4-({5-[3,5-bis(phenylmethoxy)phenyl]-1,3,4-thiadiazol-2-yl}amino)benzoic acid	B	
133		1-({3-[(5-{3-[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]phenyl}carbonyl)piperidine-4-carboxylic acid	A	
134		5-[5-(3-{3-[5-(3,4-Dichloro-phenylamino)-[1,3,4]thiadiazol-2-yl]-phenoxy}-phenyl)-tetrazol-1-yl]-pentanoic acid	B	
135		3-{[3-(5-{[3-(5-carboxypentylthio)phenyl]amino}(1,3,4-thiadiazol-2-yl))-5-(phenylmethoxy)phenoxy]methyl}benzoic acid	B	
136		N-{5-[3-(3-Trifluoromethyl-phenoxy)-phenyl]-[1,3,4]thiadiazol-2-yl}-succinamic acid	A	
137		3-[(5-{3,5-bis[3-(trifluoromethyl)phenoxy]phenyl}-1,3,4-thiadiazol-2-yl)amino]butanoic acid	B	
138		2-(N-hydroxycarbamoylmethyl)(2S)-N-{(1S)-1-[N-((1S)-1-carbamoyl-3-methylbutyl) carbamoyl]-2-naphthylethyl}-4-methylpentanamide	B	
		*LF= anthrax lethal factor. MMP1= human matrix metalloproteinase 1 activity range key:		

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		A IC_{50} > 100 micromolar		
		B 10<IC_{50}<100 micromolar		
		C 1<IC_{50}<10 micromolar		
		D 0.1<IC_{50}<1 micromolar		
		E 0.01<IC_{50}<0.1 micromolar		
		F IC_{50} < 0.01 micromolar		